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Targeting ion channels for cancer treatment: current progress and future challenges

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Abstract

Ion channels are key regulators of cancer cell pathophysiology. They contribute to a variety of processes such as maintenance of cellular osmolarity and membrane potential, motility (via interactions with the cytoskeleton), invasion, signal transduction, transcriptional activity and cell cycle progression, leading to tumour progression and metastasis. Ion channels thus represent promising targets for cancer therapy. Ion channels are attractive targets because many of them are expressed at the plasma membrane and a broad range of existing inhibitors are already in clinical use for other indications. However, many of the ion channels identified in cancer cells are also active in healthy normal cells, so there is a risk that certain blockers may have off-target effects on normal physiological function. This review describes recent research advances into ion channel inhibitors as anticancer therapeutics. A growing body of evidence suggests that a range of existing and novel Na^+ , K^+ , Ca^{2+} and Cl^- channel inhibitors may be effective for suppressing cancer cell proliferation, migration and invasion, as well as enhancing apoptosis, leading to suppression of tumour growth and metastasis, either alone or in combination with standard of care therapies. The majority of evidence to date is based on preclinical in vitro and in vivo studies, although there are several examples of ion channel targeting strategies now reaching early phase clinical trials. Given the strong links between ion channel function and regulation of tumour growth, metastasis and chemotherapy resistance, it is likely that further work in this area will facilitate the development of new therapeutic approaches which will reach the clinic in the future.

Introduction

Traditional chemotherapeutic approaches have been successfully used as cancer treatments for decades, partially due to their generalised, anti-proliferative and cytotoxic activity (DeVita and Chu, 2008). However, the lack of specificity of chemotherapy is a limiting factor in the treatment of more advanced tumours and acquired resistance. This has driven the development of targeted therapies, such as monoclonal antibodies, small molecule pathway inhibitors, immune check-point inhibitors and emerging cellular therapies (Baudino, 2015). The limitations of targeted treatments can come from their specificity, making their effectiveness tumour- or antigen-dependent, and thus potentially only applicable to a relatively small proportion of the population. A relatively underexplored area in cancer research is represented by the therapeutic targeting of ion channels and transporters (Oosterwijk and Gillies, 2014). Plasma membrane ion channels have been shown to contribute to a variety of cellular processes in addition to their role in maintaining membrane potential (V_m) and cellular osmolarity (Yang and Brackenbury, 2013, Djamgoz et al., 2014, Leslie et al., 2019). For example, as discussed in detail elsewhere in this series of Special Issues, alterations in ion flux can contribute to cellular motility, cytoskeletal rearrangements and signal transduction underpinning cellular migration (Schwab et al., 2012, Yang et al., 2020), growth and cell cycle progression (Blackiston et al., 2009, Urrego et al., 2014, Humeau et al., 2018), gene expression (Mycielska et al., 2005, Popov et al., 2012), as well as defining the extracellular environment (e.g. pH regulation (Parks et al., 2013, Wu et al., 2017)). In the tumour microenvironment, higher levels of K^+ and Na^+ have been reported, accompanied by a relatively decreased pH and hypoxic environment compared to healthy tissue (Ouwerkerk et al., 2007, Eil et al., 2016, Leslie et al., 2019). Elevated expression of a wide range of ion channels has also been associated with metastasis, reviewed extensively elsewhere (Pardo and Stuhmer, 2014, Brackenbury, 2016, Djamgoz et al., 2019). Together, these findings suggest that ion channels could serve as potential targets for anticancer therapies, particularly given the tumour-specific expression of certain channel types. Ion

channels, particularly those at the plasma membrane, present potentially attractive therapeutic targets due to their location and the fact that a broad range of existing inhibitors are already in clinical use. Given that many blockers of plasma membrane ion channels can act extracellularly, they can be screened relatively easily using electrophysiological approaches. Intracellular ion channels have also been shown to be important regulators of cancer cell metabolism, apoptosis and gene expression (Leanza et al., 2013a, Jang et al., 2015, Peruzzo and Szabo, 2019); these could similarly represent attractive targets for therapeutic inhibition.

On the other hand, given that many of the ion channels identified in cancer cells are expressed in healthy normal cells, there is a risk that these blockers may have off-target effects on normal physiological function. This review describes recent research advances into ion channel inhibitors for cancer treatment. Key Na^+ , K^+ , Ca^{2+} and Cl^- channel inhibitors are covered, followed by details on their use and effectiveness in cancer, as well as considering combining such inhibitors with standard of care therapies (Figure 1).

Na^+ Channel Inhibitors

Several classes of Na^+ channels have been shown to be aberrantly expressed in cancer cells where they regulate cell proliferation, migration, invasion and metastasis (Leslie et al., 2019). In particular, voltage gated Na^+ channels (VGSCs) are upregulated in tumour cells where their activity regulates V_m , morphological changes and metastatic behaviour (Grimes et al., 1995, Roger et al., 2003, Fraser et al., 2005, Nelson et al., 2014, Nelson et al., 2015, Yang et al., 2020). VGSCs have thus been studied as potential cancer targets (Table 1). VGSCs are important clinical targets for the treatment of epilepsy and cardiac arrhythmia (George, 2005, Mantegazza et al., 2010). Various Class 1B antiarrhythmic drugs, antiepileptic drugs and local anaesthetics have been studied in preclinical in vitro and in vivo cancer models (Martin

et al., 2015). For example, the anticonvulsant phenytoin inhibits breast cancer cell migration, tumour growth, invasion and metastasis (Yang et al., 2012, Nelson et al., 2015). Phenytoin also inhibits migration and secretory activity in prostate and lung cancer cells (Abdul and Hoosein, 2001, Fraser et al., 2003b, Onganer and Djamgoz, 2005). These results are generally supported by other studies using different VGSC-inhibiting drugs in breast cancer and other cancer types, including carbamazepine, riluzole, ranolazine and ropivacaine (Abdul and Hoosein, 2001, Abdul and Hoosein, 2002b, Yip et al., 2009, Speyer et al., 2012, Djamgoz and Onkal, 2013, Baptista-Hon et al., 2014, Driffort et al., 2014, Bugar et al., 2019, Guzel et al., 2019). It should be noted, however, that some compounds may elicit their anticancer effects through other mechanisms in addition to VGSC inhibition. For example, riluzole may prevent migration or promote apoptosis and cell cycle arrest (shown in glioma, neuroblastoma, lung, colon and prostate cancer) and inhibit autophagy (shown in pancreatic cancer) at least in part via its function as a non-competitive inhibitor of the metabolic glutamate receptor 1 (Akamatsu et al., 2009, Zhang et al., 2015, Seol et al., 2016, Lemieszek et al., 2018, Sun et al., 2019). Nonetheless, a number of studies now show that VGSC-inhibiting drugs suppress proliferation, promote apoptosis, and reduce migration, invasion and metastasis (Martin et al., 2015).

A key advantage of Class 1B antiarrhythmic drugs is that they display state-dependent binding and preferentially block VGSCs in the inactivated state (Clare et al., 2000).

Accumulating evidence suggests that cancer cells have a relatively depolarised V_m , which would mean that VGSCs present in these cells are predominantly in their inactivated state (Yang and Brackenbury, 2013). Importantly, studies have shown that VGSCs expressed in cancer cells, including $Na_v1.5$, carry a small persistent Na^+ current in the inactivated state which depolarises the V_m further and permits cytosolic Na^+ accumulation (Gillet et al., 2009, Brisson et al., 2011, Yang et al., 2012, Campbell et al., 2013, Yang et al., 2020). Further evidence suggests that this persistent Na^+ current is critical for promoting metastatic cell behaviour (Driffort et al., 2014, Nelson et al., 2015). Therefore, state-dependent VGSC

blockers which preferentially bind to VGSCs in the inactivated state are likely to selectively target tumour-expressing VGSCs whilst leaving VGSCs in other cells, e.g. cardiomyocytes and neurons, unaffected. There is, however, currently a lack of clinical data in support of this hypothesis. Although the VGSC-inhibiting drugs valproate and quinidine have been studied in clinical trials, their mode of action via Na^+ current suppression was not investigated (Raderer et al., 1993, Wheler et al., 2014). The therapeutic value of VGSC inhibitors in the context of cancer has been studied retrospectively in several observational cohort data studies (Walker et al., 2011, Fairhurst et al., 2014, Fairhurst et al., 2015, Reddy et al., 2015, Fairhurst et al., 2016, Takada et al., 2016). However, the results are inconsistent, with several studies demonstrating positive associations (Exadaktylos et al., 2006, Biki et al., 2008, Walker et al., 2011, Reddy et al., 2015, Takada et al., 2016) and another study showing a negative association, although the possibility of confounding by indication cannot be excluded (Fairhurst et al., 2015). Thus, prospective clinical trials are required to establish the utility of VGSC inhibition in cancer patients (Djamgoz et al., 2019).

Novel compounds have also been investigated as potential inhibitors of VGSC function in cancer cells. Novel α -hydroxy- α -phenylamide analogues of phenytoin have been developed in order to improve VGSC subtype specificity and some of these have been shown to inhibit prostate cancer cell proliferation (Anderson et al., 2003, Lenkowski et al., 2004). Additional small molecule VGSC inhibitors have been developed with the aim of increasing selectivity for the neonatal splice variant of $\text{Na}_v1.5$ expressed in breast cancer cells and these have been shown to inhibit both Na^+ current and invasion (Dutta et al., 2018). The casein kinase 1 inhibitor IC261, which induces cell cycle arrest and apoptosis in cancer cell lines, has also been shown to inhibit $\text{Na}_v1.5$ currents, suggesting that IC261 may elicit its anti-tumour effects partially through VGSC inhibition (Brockschmidt et al., 2008, Föhr et al., 2017). The mexiletine analogue RS10064, targeted at tetrodotoxin-resistant VGSCs, inhibits oxidative stress induced by tumour development in the DMBA rat breast cancer model (Batcioglu et al., 2012). ω -3 polyunsaturated docosahexaenoic acid, which has been shown to improve breast

cancer outcomes, inhibits Na_v1.5 expression and activity in breast cancer cells via peroxisome proliferator-activated receptor β (PPAR β) (Isbilen et al., 2006, Gillet et al., 2011, Wannous et al., 2015).

Numerous peptide toxins bind to and inhibit VGSCs, and several of these have been explored in the context of cancer treatment. Local injection of the pan-specific VGSC-inhibiting toxin tetrodotoxin directly into subcutaneous prostate tumours in rats significantly reduces lung metastasis, improving survival (Yildirim et al., 2012). Treatment of prostate cancer cells with the tarantula peptide toxin HNTX-III derived from the venom of *Selenocosmia hainana* downregulates Na_v1.7, decreases RhoA/Rac1 protein expression and inhibits cellular migration, raising the possibility that such isoform-specific toxins may have utility as anti-motility drugs (Chen et al., 2019). However, a potential issue with peptide toxins such as tetrodotoxin is that, unlike Class 1B antiarrhythmic drugs, they do not display state-dependent binding. Thus, it would not be possible to administer such agents systemically without toxic side-effects. Nonetheless, chemical modification of these toxins to aid tumour-specific targeting may be possible. One further issue with the use of VGSC inhibitors in general, including state-dependent blockers, is that they may also inhibit VGSCs present on immune cells, potentially reducing a desirable anti-tumour immune response. For example, Na_v1.5 is expressed on CD4⁺ T cells where it plays a role in positive selection (Lo et al., 2012).

There has also been interest in developing ion-channel targeting monoclonal antibodies. This has proven to be relatively challenging given the complex structure of ion channel proteins, which makes it difficult to identify suitable epitopes, as well as due to the complexity of manufacturing antibodies, compared to small molecule design (Hutchings et al., 2019). A polyclonal antibody directed at the neonatal Na_v1.5-specific D1:S3/4 linker inhibits Na⁺ current with high specificity for neonatal Na_v1.5 versus the adult splice variant (Chioni et al., 2005). Importantly, this antibody was additionally shown to inhibit migration and invasion of

breast cancer cells (Brackenbury et al., 2007). Although the primary purpose of such antibodies has been to inhibit channel function, an additional possibility is that these antibodies may have utility as diagnostic tools (Yamaci et al., 2017) and/or as vehicles to target cytotoxic therapies to tumours (Arcangeli et al., 2009).

Epithelial Na^+ channels (ENaC) from the ENaC/degenerin family are also important players in metastatic cell behaviour (Yamamura et al., 2008, Bondarava et al., 2009, Del Monaco et al., 2009, Kapoor et al., 2009, Xu et al., 2016). ENaC activity promotes proliferation and inhibits apoptosis of hepatic carcinoma cells, as part of a hypertonicity-induced cationic channel complex (Sparks et al., 1983, Vila-Carriales et al., 2006, Bondarava et al., 2009). More recently, ENaC expression has been associated with increased expression of the achaete-scute homolog 1 (ASCL-1) transcription factor that mediates growth and progression of lung tumours (He et al., 2018). The exact mechanism that connects ENaC and ASCL-1 has not been fully defined, but these findings suggest that ENaC might contribute to tumour growth as a transcriptional target of ASCL-1 (He et al., 2018). Acid-sensing ion channels (ASIC), also members of the ENaC/degenerin family, can enhance invasive behaviour by activating the calcineurin/Nuclear Factor of Activated T Cells 1 (NFAT1) pathway in colorectal cancer cells and treatment with cyclosporin A was shown to block the calcineurin pathway and ASIC2-mediated metastasis (Zhou et al., 2017). ASIC1 and 3 promote epithelial to mesenchymal transition in pancreatic cancer cells in a Ca^{2+} -dependent manner (Zhu et al., 2017). The ENaC-inhibiting K^+ -sparing diuretic amiloride has been shown to suppress ENaC-induced chorionic carcinoma cell migration in response to aldosterone (Del Monaco et al., 2009). Together with further studies showing anti-tumour and anti-metastatic effects of amiloride, these data suggest that pharmacological blockade of ENaC/ASIC channels may have therapeutic relevance (Matthews et al., 2011).

The ATP-dependent Na^+/K^+ pump (also known as the Na^+/K^+ ATPase) is an important regulator of Na^+/K^+ homeostasis in cancer cells (Zhang et al., 2008, Schneditz et al.,

2019). This pump is the key membrane protein for transporting Na^+ out from the cell and maintaining a stable V_m (Post et al., 1969). Na^+/K^+ ATPase expression is elevated in breast cancer cells compared to normal epithelial cells and its activity promotes proliferation, migration and invasion (Li et al., 2017, Khajah et al., 2018). Different Na^+/K^+ ATPase α subunit isoforms have been associated with cancer malignancy: $\alpha 1$ mostly correlates with early stages of cancer (including prostate, lung and renal tumours), whilst $\alpha 3$ associates with advanced disease (Felippe Goncalves-de-Albuquerque et al., 2017). Cardiac glycoside digitalis drugs, e.g. ouabain, digoxin, which are potent inhibitors of the Na^+/K^+ ATPase (Post et al., 1969, Laursen et al., 2013), have been shown to inhibit proliferation, migration, invasion, inflammation, tumour growth and promote lysis of cancer cells (Zhang et al., 2008, Kepp et al., 2012, Gould et al., 2018, Khajah et al., 2018), reduce risk of certain cancers (Haux et al., 2001) and improve survival (Menger et al., 2012). Inhibition of the Na^+/K^+ ATPase by digitalis drugs leads to intracellular accumulation of Na^+ and subsequent reverse mode operation of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX) causing an increase in intracellular Ca^{2+} , which may then impact on cell cycle progression and survival (Chen et al., 2014). Interestingly, studies have shown that while the ion transport function of the Na^+/K^+ ATPase is inhibited by cardiac glycosides, these can enhance signalling via the pump, inducing activation of an associated kinase – Src, which transactivates the epidermal growth factor receptor (EGFR), forming a signalling complex that induces activation of mitogen-activated kinase (MAPK), thus indicating a complex function of the Na^+/K^+ pump in maintaining cellular physiology (Haas et al., 2002). Although the Na^+/K^+ ATPase was long thought to be the only target of ouabain and other digitalis drugs, there is emerging evidence suggesting that these compounds modulate additional targets, such as the X-hepatic receptor (Campia et al., 2012) and the steroid receptor co-activators (SRC) 1 and 3 (Wang et al., 2014). Thus, effects on cancer cells following treatment with these drugs might be derived from their impact on other targets.

In summary, a growing body of evidence suggests that pharmacological inhibition of various classes of Na⁺ channels and transporters in cancer cells can inhibit proliferative and invasive capacity and may promote cell death. Further work is required to fully delineate the mechanism(s) of action of a number of these compounds in cancer cells and their potential clinical value.

K⁺ Channel Inhibitors

Many plasma membrane K⁺ channels are aberrantly expressed in cancer cells where their expression is often associated with increased proliferative capacity, and a number of these have been explored as therapeutic targets (Table 2) (Huang and Jan, 2014, Pardo and Stuhmer, 2014). For example, the K_v1.3 voltage-gated K⁺ channel (VGKC) plays a role in regulation of proliferation in brain cell progenitors, but also in cancer cells (Fraser et al., 2000, Chittajallu et al., 2002, Fraser et al., 2003a). In prostate cancer cells, K_v1.3 was shown to be sensitive to several drugs, including dequalinium, glyburide and amiodarone, which induced growth inhibition and cell death (Abdul and Hoosein, 2002a). In addition, K_v1.3 currents in prostate cancer cells are sensitive to verapamil, margatoxin, charybdotoxin, 4-aminopyridine and tetraethylammonium (Fraser et al., 2003a). In melanoma cells, treatment with the K_v1.3 inhibitors tetraethylammonium, verapamil and fampridine was shown to disrupt the interaction between K_v1.3 channels and β1 integrin, suggesting that integration of VGKCs in macromolecular protein complexes might provide a role in tumour cell adhesion and invasion (Artym and Petty, 2002).

Another VGKC widely studied in the context of cancer is Eag1 (K_v10.1) (Ouadid-Ahidouch et al., 2016). K_v10.1 is upregulated in a number of tumour types (Ding et al., 2007, Ousingsawat et al., 2007). K_v10.1 promotes proliferation in cancer cell lines and over-expression in Chinese hamster ovary cells causes tumorigenesis in vivo (Pardo et al., 1999, Ouadid-

Ahidouch et al., 2001). Direct targeting of K_v10.1 with monoclonal antibodies inhibits K⁺ currents and has an anti-proliferative effect, reducing tumour growth in vivo (Gómez-Varela et al., 2007). Furthermore, development of a bifunctional antibody carrying a human K_v10.1 recognition site and a human TNF-related apoptosis-inducing ligand (TRAIL) domain was shown to induce selective apoptosis in prostate cancer cells sensitised with cytotoxic drugs (Hartung et al., 2011). Other well-established inhibitors of human Eag1 include astemizole and imipramine (Garcia-Ferreiro et al., 2004). Imipramine was shown to inhibit proliferation and induce apoptotic behaviour in ovarian cancer cells (Asher et al., 2011). Astemizole has also been shown to inhibit proliferation in vitro and tumour growth in vivo (Garcia-Quiroz and Camacho, 2011, de Guadalupe Chavez-Lopez et al., 2015, Bernal-Ramos et al., 2017). In addition, the sea anemone toxin APETx4 inhibits K_v10.1, although it is cytotoxic in both cancer and non-cancer cell lines (Moreels et al., 2017b). Several novel purpurealidin analogues were also found to inhibit K_v10.1 current and increase cell death (Moreels et al., 2017a).

HERG (K_v11.1) is primarily associated with cardiac arrhythmias, but is also upregulated in various cancers (Cherubini et al., 2000, Pillozzi et al., 2002, Lastraioli et al., 2004, Lastraioli et al., 2006). As with K_v10.1, K_v11.1-mediated K⁺ current has been shown to increase cancer cell proliferation (Bianchi et al., 1998, Wang et al., 2002, Arcangeli, 2005). In addition, K_v11.1 interacts with β 1 integrin, promoting adhesion interactions and adhesion-dependent signalling to regulate cancer cell survival, migration, invasion and chemoresistance (Cherubini et al., 2005, Arcangeli and Becchetti, 2006, Pillozzi et al., 2007, Pillozzi et al., 2011, Crociani et al., 2013). K_v11.1 has been studied as a potential cancer target and anti-cancer agents, e.g. tamoxifen, have been shown to have an inhibitory effect on channel function (Thomas et al., 2003). The K_v11.1 inhibitor cisapride has also been shown to inhibit proliferation of gastric cancer cells (Shao et al., 2005). In addition, the K_v11.1 inhibitor E4031 reduced infiltration of acute lymphoblastic leukaemia cells in a mouse model, increasing survival (Pillozzi et al., 2011). E4031 and another K_v11.1 inhibitor (WAY123,398) also

suppress gastric and colorectal cancer growth, angiogenesis (by PI3K/ β 1-integrin-mediated Akt activation leading to vascular endothelial growth factor (VEGF)-A transcription) and metastasis in mice (Crociani et al., 2013, Crociani et al., 2014). E4031 was also shown to inhibit colon cancer cell proliferation and $K_v11.1$ was identified as a biomarker of colon cancer in patient samples (Dolderer et al., 2010). E4031 and a second $K_v11.1$ inhibitor, ergtoxin, were shown to inhibit proliferation of ovarian cancer cells by inhibiting cell cycle progression, but without inducing apoptotic behaviour (Asher et al., 2011). A potential issue with the use of $K_v11.1$ blockers is the risk of off-target effects, specifically slowed cardiac repolarization and ventricular arrhythmia (Arcangeli et al., 2009). However, this may be overcome by the use of state-dependent blockers targeting $K_v11.1$ in the open state in cancer cells, whilst leaving cardiac $K_v11.1$ channels in the inactivated state unaffected (Arcangeli et al., 2009). $K_v11.1$ -targeting monoclonal antibody-nanoparticle conjugates have also been explored as potential vehicles to deliver photodynamic therapies for pancreatic cancer (Sette et al., 2013) and novel recombinant anti- $K_v11.1$ single chain fragment variable antibodies have been developed and evaluated for cancer molecular imaging (Duranti et al., 2018, Duranti and Arcangeli, 2019).

The K^+ 2 pore domain (K_{2P}) channels, which contribute to setting the resting V_m , are also upregulated in a variety of cancers including breast, colon, prostate and lung tumours and have been shown to promote proliferation (Mu et al., 2003, Kim et al., 2004, Voloshyna et al., 2008). However, some members of this family appear to be downregulated in other tumour types, suggesting a complex function of K_{2P} channels in cancer progression (Williams et al., 2013). A monoclonal antibody against the extracellular domain of $K_{2P9.1}$ has been shown to inhibit tumour growth and metastasis in mice (Sun et al., 2016). Ca^{2+} -activated K^+ channels are also expressed in cancer cells (Brackenbury, 2016). The large conductance $K_{Ca1.1}$ channel promotes proliferation of HeLa cervical cancer cells, and this can be inhibited by treatment with the $K_{Ca1.1}$ blocker iberiotoxin (Han et al., 2007). In addition, iberiotoxin causes cell cycle arrest and apoptosis in glioma cells (Weaver et al., 2004). The vitamin D receptor

agonists calcitriol and calcipotriol, and the androgen receptor antagonists bicalutamide and enzalutamide inhibit $K_{Ca}1.1$ expression in breast cancer cells, suggesting that these compounds may also elicit antiproliferative activity via $K_{Ca}1.1$ inhibition (Khatun et al., 2016, Khatun et al., 2018). The intermediate conductance $K_{Ca}3.1$ channel blocker TRAM-34 inhibits cell cycle progression of B lymphoma cells induced by serum (Wang et al., 2007). The same study also showed that the CD20-targeting monoclonal antibody rituximab also inhibits $K_{Ca}3.1$ activity (Wang et al., 2007). Similarly, TRAM-34 inhibits proliferation and migration and promote apoptosis of breast cancer cells (Zhang et al., 2016). TRAM-34 also inhibits $K_{Ca}3.1$ -mediated glioma cell migration and invasion (Turner et al., 2014). In addition, $K_{Ca}3.1$ overexpression in breast cancer cells promotes tumour growth and metastasis (Thurber et al., 2017). However, in pancreatic cancer cells, although TRAM-34 inhibited $K_{Ca}3.1$ currents, it actually promoted migration and invasion, suggesting potential anomalous effects of this compound and/or target (Bonito et al., 2016). Inhibition of small conductance $K_{Ca}2.3$ channels with tetraethylammonium, apamin and 4-aminopyrimidine decreased breast cancer cell migration in vitro (Potier et al., 2006) and recently new lipophilic pyridine and tetrahydropyridine derivatives have been designed and synthesised which inhibit $K_{Ca}2.3$ channel activity and cellular migration (Kouba et al., 2020).

Targeting intracellular K^+ channels may also derive benefit. Mitochondrial $K_v1.3$ is widely expressed in various tissues, and a nuclear $K_v1.3$ was also identified in some breast, lung and gastric adenocarcinoma cell lines, as well as in lymphocytes and brain cells. Nuclear $K_v1.3$ functions as a regulator of gene expression by interacting with the cAMP response element-binding protein (CREB) and the c-FOS transcription factors (Jang et al., 2015). Mitochondrial $K_v1.3$ interacts with the Bcl-2 family protein, Bax, which inhibits the activity of the channel, inducing cytochrome c cytoplasmic release and subsequent apoptosis (Szabó et al., 2008, Szabó et al., 2011). Pharmacological inhibition of intracellular $K_v1.3$ with Psora-4, clofazimine and 5-(4-Phenoxybutoxy)psoralen (PAP1) induces apoptosis in lymphocyte, fibroblast, bone, skin cancer cell lines in a Bax/Bak-independent manner. Furthermore, the

same inhibitors induce apoptosis in patient-derived leukaemia B cells and clofazimine reduces melanoma tumour growth in vivo (Leanza et al., 2012, Leanza et al., 2013b).

K_v10.1 is also expressed in the nuclear membrane of malignant brain colon and ovarian cancer cells, as well as leukaemia and fibrosarcoma (Martínez et al., 2015, Peruzzo et al., 2016). Given its location, it has been suggested that K_v10.1 might also impact on gene expression. However, unlike K_v1.3 its pro-tumorigenic function seems to occur through changes in channel conformation rather than through K⁺ transport (Hegle et al., 2006, Chen et al., 2011). K_{Ca}3.1 and VGKCs have also been identified in mitochondria of melanoma, colon and breast cancer cells where they regulate oxidative phosphorylation and proliferation (Kovalenko et al., 2016). Combined activation of membrane and mitochondrial K_{Ca}3.1 is associated with breast tumour resistance to radiotherapy in vivo (Mohr et al., 2019). In addition, intracellular K_{Ca}3.1 is sensitive to inhibition by TRAM-34 and clotrimazole (De Marchi et al., 2009). Elevated intracellular K_{Ca}1.1 has been reported in the endoplasmic reticulum (ER), nucleus and Golgi of pancreatic cancer cells (Singh et al., 2012). Bax-mediated inhibition of mitochondrial K_{Ca}1.1 promotes apoptosis by enhancing the formation of the mitochondrial permeability transition pore (Cheng et al., 2011). The mitochondrial acid sensing K⁺ channel, TASK3, mediates survival and maintains mitochondrial integrity in melanoma cells (Kosztka et al., 2011, Nagy et al., 2014). Furthermore, inhibition of TASK3 with Zn²⁺ or methanandamide slows proliferation of ovarian cancer cells, suggesting that it might serve as a valuable target (Innamaa et al., 2013).

In summary, various classes of plasma membrane and intracellular K⁺ channels are upregulated in cancer cells and a number of studies point to pharmacological inhibition of specific subtypes as an effective approach to suppress proliferation, migration and invasion, and increase apoptosis.

Ca²⁺ Channel Inhibitors

A number of different types of plasma membrane Ca²⁺ channel have been documented in cancer cells that could be targeted therapeutically (Table 3) (Lee et al., 2011, Prevarskaya et al., 2011, Bong and Monteith, 2018, Gautier et al., 2019). Upregulation of L-type (Ca_v1.x) and T-type (Ca_v3.x) voltage-gated Ca²⁺ channels promotes differentiation, secretion of mitogenic factors, proliferation and angiogenesis (Bertolesi et al., 2002, Mariot et al., 2002, Sun et al., 2006, Gackiere et al., 2008, Lu et al., 2008). Emerging preclinical evidence suggests that repurposing Ca_v channel-inhibiting drugs to cancer may be beneficial (Buchanan and McCloskey, 2016). For example, mibefradil and the Ca_v3.x inhibitor NNC-55-0396 have been shown to reduce cell proliferation and induce cell apoptosis in leukaemia cell lines (Huang et al., 2015). Inhibition of Ca_v1.3 in endometrial carcinoma cells with nifedipine reduced proliferation and migration and induced autophagy (Bao et al., 2012). Nifedipine has also been shown to inhibit proliferation of breast cancer cells (Squecco et al., 2015). In addition, the Ca_v3.x blocker KYS05090 has been shown to induce apoptosis and autophagy in lung cancer cells, although the mechanism may be channel independent (Rim et al., 2014).

The store operated Ca²⁺ channel proteins also play an oncogenic role (Yang et al., 2009). ORAI1 and ORAI3 heterodimerise to support Ca²⁺ influx and promote proliferation (Dubois et al., 2014). Furthermore, the store operated Ca²⁺ channel blocker SKF96365 inhibits breast cancer metastasis in mice (Yang et al., 2009). Various transient receptor potential (TRP) channels, activated by extracellular stimuli e.g. pH, mechanical stimuli, are also expressed in cancer cells and can promote proliferation, survival angiogenesis and metastasis (Thebault et al., 2006, Bidaux et al., 2007, Lehen'kyi et al., 2007, Bolanz et al., 2008, Bomben and Sontheimer, 2008, Guilbert et al., 2009, Fiorio Pla et al., 2012). However, there are some exceptions, e.g. TRPM6, which is downregulated in colorectal tumours and associates with improved survival (Xie et al., 2018) and TRPM8, which inhibits migration (Genova et al., 2017). Treatment of breast cancer cells with the TRP channel inhibitor 2-

aminoethoxydiphenyl borate (2-APB) has been shown to decrease proliferation by damaging DNA (Hopkins et al., 2015). The specific TRPM7 inhibitor waixenicin A significantly decreased colon cancer cell proliferation in vitro but had no impact on aberrant crypt foci development in vivo, highlighting the importance of model selection in screening of channel inhibitors (Huang et al., 2017). In addition, given the complex involvement of various TRP channel subtypes in promoting/inhibiting cancer progression, channel inhibition will not be appropriate in certain circumstances. For example, the TRPM8 agonist WS12 suppresses endothelial cell migration and prostate cancer metastasis in mouse models (Genova et al., 2017, Grolez et al., 2019). Nonetheless, TRP channel inhibitors have been studied in the clinical setting. The TRPV6 inhibitor SOR-C13 recently went into first-in-human phase I study in patients with advanced solid tumours and disease stabilisation in the treated cohort suggested potential anti-tumour activity (Fu et al., 2017).

The purinergic P2X7 cation channel has also gained interest in the context of cancer, although conflicting results from different studies have been challenging to interpret (Roger et al., 2015). However, a monoclonal antibody targeting a unique epitope on the cancer-specific variant of P2X7 (nfP2X7) has undergone Phase 1 clinical trial for basal cell carcinoma with promising results including disease stabilisation, partial and complete response (Gilbert et al., 2017, Gilbert et al., 2019).

In colon cancer cells, the cannabinoid cannabigerol suppresses proliferation and promotes reactive oxygen species (ROS) production and apoptosis via TRPM8 inhibition, and slows tumour growth in vivo (Borrelli et al., 2014). In addition, upregulation of TRPV1 has been identified as a key player in cannabinoid-derivative-induced apoptosis of cervical cancer and glioma cells (Contassot et al., 2004a, Contassot et al., 2004b). Other studies, however, propose different mechanisms for the anti-cancer activity of cannabinoids (Hamtiaux et al., 2011), for example, by interacting with the cannabinoid receptor 2 in addition to TRPV1 activation (Ligresti et al., 2006).

Intracellular Ca^{2+} channels may also present potential targets. For example, TRPM8 and TRPC1 both play a role in survival and proliferation of tumour cells (Zhang and Barritt, 2004, Shapovalov et al., 2016). TRPM8 inhibition with capsazepine reduces survival of prostate cancer cells, and TRPM8 knockdown slows proliferation of osteosarcoma cells by interfering with Ca^{2+} -dependent Akt function (Zhang and Barritt, 2004, Wang et al., 2013). TRPC1 regulates glioma cell division and its inhibition with 2-APB, MRS-1845 and SKF96365 inhibits proliferation in vitro and reduces tumour size in mouse models (Bomben and Sontheimer, 2010). Ryanodine receptors promote breast cancer cell survival and their expression correlates with tumour grade; in addition, the ryanodine receptor inhibitor 4-chloro-m-cresol inhibits breast cancer cell proliferation in vitro (Abdul et al., 2008). Furthermore, treatment of lung cancer cells with the ryanodine receptor inhibitor 20-O- β -D-glucopyranosyl-20(S)-protopanaxadiol induces Ca^{2+} -dependent apoptosis, supporting the essential role of these channels in cancer cell survival (Shin et al., 2018).

In summary, a number of Ca^{2+} channel inhibitors have shown promise in preclinical studies and some of these have now reached clinical trials. Several epidemiological studies show that existing Ca^{2+} channel blockers are not associated with increased cancer risk (Grimaldi-Bensouda et al., 2016, Wilson et al., 2016, Brasky et al., 2017), supporting a compelling argument for further exploration of the possibility of repurposing such drugs to treat cancer (Buchanan and McCloskey, 2016). However, the complex opposing roles of some Ca^{2+} channels in cancer cells, e.g. certain TRP and P2X7 channels, highlights the importance of fully understanding their diverse physiological roles in order to permit appropriate targeting.

Cl⁻ Channel Inhibitors

Several Cl⁻ channels have been shown to be aberrantly expressed in cancer cells, contributing to survival and progression and some have been explored as therapeutic targets (Table 4). The ionotropic Cl⁻-permeant GABA_A receptor is upregulated on metastatic breast cancer cells in the brain (Neman et al., 2014), which themselves promote altered regional excitability (Simon et al., 2020). The voltage-gated Cl⁻ channels CLC-2 and CLC-3 are functionally active in glioma cells and the latter is essential for facilitating mitosis and invasion by regulating cell volume (Olsen et al., 2003, Habela et al., 2008, Lui et al., 2010, Watkins and Sontheimer, 2011). CLC-3 also stimulates breast cancer cell proliferation and tumour growth (Zhou et al., 2018) and promotes migration of nasopharyngeal carcinoma cells (Mao et al., 2008). However, other studies have indicated that CLC-3 can also promote apoptosis (Liu et al., 2013), thus cancer-promoting or inhibiting activity of this channel is likely finely tuned and may be context dependent (Hong et al., 2015). CLC-3 is sensitive to non-specific Cl⁻ channel inhibitors such as tamoxifen and 4-5-nitro-2-(3-phenylpropylamino) benzoic acids (NPPBs) (Wang et al., 2012), inhibiting cancer cell proliferation (Shen et al., 2000). Similarly, tamoxifen was shown to only have an inhibitory effect on cancer cell migration in the presence of CLC-3, likely as a result of dysregulated cell volume management and therefore cell cycle stagnation (Mao et al., 2013).

Hydrolysis products of 4,4-diisothiocyanatostilbene-2,2'-disulfonic acid (DIDS), which are inhibitors of anion permeability, can inhibit CLC family channels, as can phenylalanine derivatives (stilbenes), clofibric acids, benzofurans, and the newer benzimidazole derivative, BIM1 (Matulef et al., 2008, Koster et al., 2018). However, the broad effect of such compounds on other Cl⁻ channels remains a challenge with respect to potential off-target effects (Hong et al., 2015) and applicability in cancer treatment needs to be confirmed through further studies. Specific function-blocking antibodies targeting CLC-3 have been developed (Wang et al., 2003) but their efficacy in cancer models remains to be determined. Chlorotoxin, a scorpion toxin identified as a CLC-3 inhibitor, binds to a membrane-bound matrix metalloproteinase on glioma cells (Deshane et al., 2003). Radiolabelled I¹³¹-

chlorotoxin has undergone a Phase 1 clinical trial in adult patients with high grade glioma with the aim of improving targeted radiation to the tumour site and demonstrated good tolerability and potential anti-tumoral effects (Mamelak et al., 2006).

The anoctamin Ca^{2+} -dependent Cl^- channels promote cancer cell proliferation and apoptosis of cancer cells under certain conditions (Kunzelmann et al., 2019). Inhibition of ANO1/TMEM16 with the specific inhibitor CaCCinh-A01 significantly decreased tumour progression, raising the possibility that this channel may be a potential therapeutic target (Britschgi et al., 2013). An important regulator of the Cl^- concentration within developing glial cells is the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter (NKCC1). NKCC1 has been proposed as a key promoter of glioma cell migration, being localized at the tip of the migratory pole of the cell and also influences cell-cell adhesion and Cl^- -dependent cell volume regulation (Habela et al., 2009, Garzon-Muvdi et al., 2012). Treatment with the NKCC1 inhibitor bumetanide inhibits migration of metastatic glioma cells both in vivo and in vitro, suggesting that NKCC1 could be a promising target in the treatment of glioma (Haas and Sontheimer, 2010).

In lung cancer cells, the Cl^- intracellular channel 1 (CLIC1), which can be found both at the plasma membrane and in the cytosol, suppresses Ca^{2+} import via L-type Ca^{2+} channels, promoting survival (Lee et al., 2019b). In silico analysis showed a much higher risk of death in breast, pancreatic and liver cancer patients with high CLIC1 expression, while gastric cancer patients with high CLIC1 levels have a survival advantage, suggesting that its function might vary with depending on tumour type (Gururaja Rao et al., 2020). Further work is required to establish the therapeutic value of CLIC1 inhibition, and/or inhibition of other intracellular Cl^- channel subtypes, e.g. CLIC4 (Fernández-Salas et al., 2002, Zhong et al., 2012).

In summary, both plasma membrane and intracellular Cl^- channels are important regulators of cell cycle, proliferation and migration, making them promising targets for cancer therapies.

Although some inhibitory molecules have been found effective in reducing tumour cell growth and migration, there is a strong potential for developing more specific inhibitors, targeted at both intracellular and extracellular channels.

Combinatorial Treatments

The fact that a number of ion channel-targeting drugs inhibit cellular functions including proliferation, migration and invasion, and that others promote apoptosis, raises the possibility that such compounds may have utility in combination with standard of care therapies, e.g. chemotherapy. Furthermore, perturbation of the ionic balance within tumour cells may provide favourable conditions for the intracellular partitioning of certain cytotoxic drugs, enhancing their effectiveness. For example, in triple negative breast cancer cells, β -adrenergic receptors and $\text{Na}_v1.5$ colocalise and the β -adrenergic receptor competitive antagonist propranolol and the VGSC inhibitor ranolazine decrease Na^+ currents, migration and invasion both when administered individually and in combination (Lee et al., 2019a). Downregulation of $\text{K}_v10.1$ with shRNA or application of the $\text{K}_v10.1$ inhibitor astemizole to glioblastoma cells sensitises them to treatment with the standard of care chemotherapeutic temozolomide (Sales et al., 2016). Combination of astemizole with gefitinib has been shown to synergistically increase apoptosis of lung cancer cells over treatment with either agent alone (Chavez-Lopez et al., 2017). Another example is the macrolide antibiotics, which have antileukemic activity alone and in combination with chemotherapeutic drugs, and this was shown to be due to $\text{K}_v11.1$ inhibition (Pillozzi et al., 2016).

Riluzole has been shown to inhibit $\text{K}_v11.1$ and activate $\text{K}_{Ca3.1}$ in colon cancer cells, thus contributing to cisplatin uptake (Pillozzi et al., 2018). Combined administration of the $\text{K}_{Ca3.1}$ activator SKA-31 and E4031 had a similar effect, which was reproducible in mouse models, suggesting a complex interplay between $\text{K}_{Ca3.1}$ and $\text{K}_v11.1$ (Pillozzi et al., 2018). Riluzole

has also been shown to activate the K_{2P} channel (TREK-1), reducing neuropathic pain and depression-like symptoms induced by treatment with oxaliplatin in colon cancer mouse models (Poupon et al., 2018). Another potentially interesting combinatorial treatment is represented by the $K_{2P3.1}$ and $K_{2P9.1}$ channel inhibitors anandamide and ruthenium red, which have been shown to additively inhibit K^+ currents in lung cancer cells, although the effect of these compounds on cell proliferation was not determined (Leithner et al., 2016).

Inhibitors of Ca^{2+} channels have also been investigated for combinatorial therapies. The $Ca_v3.x$ antagonist mibefradil has been shown to inhibit glioblastoma stem-like cell proliferation in vitro and tumour growth in a glioblastoma mouse model, and sensitises tumours to treatment with temozolomide (Zhang et al., 2017b). Pharmacological inhibition of $Ca_v3.x$ channel activity with the antagonists mibefradil and pimozide also synergistically suppressed proliferation in several cancer cell lines (Bertolesi et al., 2002). Inhibition of active ion transport may also be beneficial in combinatorial treatments. For example, suppression of plasma membrane Ca^{2+} ATPase isoform 2 (PMCA2) expression was shown to inhibit proliferation of breast cancer cells on its own, as well as enhancing the cytotoxicity of doxorubicin (Peters et al., 2016). Store operated Ca^{2+} entry induces expression of the chemotherapy resistance marker MDR1 in breast cancer cells (Babaer et al., 2018). Knock down of ORAI1 or STIM1 thus significantly increases sensitivity to chemotherapeutic drugs including cisplatin, gentamycin and 5-fluorouracyl (Kondratska et al., 2014, Sun et al., 2017, Kischel et al., 2019). Similarly, inhibition of TRPC5, either by siRNA or by treatment with chloroquine or 3-methyladenine, increases sensitivity to doxorubicin in breast cancer cell lines (Zhang et al., 2017a). On the other hand, different studies suggest certain Ca^{2+} channels render cells more responsive to chemotherapy (Kischel et al., 2019). For example, TRPC1 expression is downregulated in drug-resistant ovarian cancer tissues compared with drug-responsive samples and cisplatin and carboplatin-resistant ovarian cancer cell lines were shown to also have lower levels of TRPC1 (Liu et al., 2016). TRPV2 activation with cannabidiol plays an important role in sensitising glioma cells to doxorubicin, carmustine and

temozolomide (Nabissi et al., 2012). Thus, combination of certain channel-modulating drugs and chemotherapeutic drugs may have value by reducing tumour chemotherapeutic resistance, but the situation is likely channel or cell-type dependent.

Ion channel inhibition may also be advantageous in the context of standard of care radiotherapy. For example, antiepileptic drug use is associated with improved overall survival of breast cancer patients with brain metastasis receiving whole brain radiotherapy (Reddy et al., 2015), raising the possibility that VGSC inhibition may radiosensitise brain metastases. In addition, TRPM8 inhibition has been shown to radiosensitise glioblastoma cells and attenuate DNA repair (Klumpp et al., 2017) and TRPM2 inhibition enhances radiotherapy-induced cell death in leukaemia cells (Klumpp et al., 2016).

By targeting specific ion channels, certain inhibitors may enhance the capacity of the immune system to fight tumours. For example, non-small cell lung cancer patients with low serum salt levels respond poorly to immune check-point inhibitor therapy, illustrating potential interconnection between ionic balance and immune system-mediated tumour clearance (Fuca et al., 2018). Another study showed that an increase in extracellular K^+ caused by tumour cell necrosis has an immunosuppressive impact on effector T cells by increasing intracellular K^+ . Upregulation of $K_v1.3$ in T cells resulted in K^+ export, counteracting the immunosuppressive action of the tumour-derived K^+ (Eil et al., 2016). Furthermore, high K^+ in the tumour microenvironment maintained T cells in a stem-like state capable of dividing and enhancing tumour destruction (Vodnala et al., 2019). These data suggest manipulation of K^+ flux may be effective in enhancing immunotherapeutic approaches.

In summary, considerable research has been carried out towards combining current cancer therapies and ion channel inhibitors or developing new combinatorial treatments that integrate ionic targeting. Despite significant progress, there is yet much that needs to be

done to optimise and refine existing therapies, as well as to generate new and effective strategies for exploiting ionic imbalances in the tumour microenvironment.

Conclusions and Future Perspectives

The study of ion channel inhibitors in the context of oncology is gaining interest with time, particularly given the limitation of chemotherapy and targeted therapies, and the need for new perspectives on counteracting tumour progression and metastasis. Whilst individual ion channel targeting may be effective on its own in certain circumstances, a combinatorial approach of ion channel-targeting drugs and chemotherapy, radiotherapy and/or emerging immunotherapies may derive greater benefits. However, a key obstacle remains in terms of tumour specificity, given that many of these channels are also expressed in normal cells. Therefore, the use of ion channel blockers can often be accompanied by severe side effects and might even be lethal (Vandenberg et al., 2012).

Engineering antibodies or small molecules that target tumour-specific isoforms/states of various ion channels has been a step forward towards increasing the sensitivity and specificity of ion channel-targeted therapies in cancer (Clare et al., 2000, Chioni et al., 2005, Hartung et al., 2011, Sette et al., 2013, Sun et al., 2016, Gilbert et al., 2017). Yet, the continuous dynamics of the tumour environment could limit the efficacy of these approaches through target mutations. Furthermore, antibody therapies are limited both by the size-dependent tissue penetration and by the manufacturing procedure. Nevertheless, the idea of specifically targeting tumour-associated ion channels is worth investigating for the future. The capacity to distinguish between malignant and healthy ion channels could enable more complex therapeutic approaches such as combining ion channels inhibitors that could suppress tumour growth and ion channel enhancers that would induce activation and proliferation of immune cells, enabling those to clear the malignant tissue (Chiang et al.,

2017). However, before such complex strategies can be designed a more complete understanding of tumour-specific ion channel expression, function and pharmacology is required.

In conclusion, given the strong links between ion channel function and regulation of tumour growth, metastasis and chemotherapy resistance, it is likely that further work in this area will facilitate the development of new, multilateral therapeutic approaches.

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References

- ABDUL, M. & HOOSEIN, N. 2001. Inhibition by anticonvulsants of prostate-specific antigen and interleukin-6 secretion by human prostate cancer cells. *Anticancer Res*, 21, 2045-8.
- ABDUL, M. & HOOSEIN, N. 2002a. Expression and activity of potassium ion channels in human prostate cancer. *Cancer Letters*, 186, 99-105.
- ABDUL, M. & HOOSEIN, N. 2002b. Voltage-gated sodium ion channels in prostate cancer: expression and activity. *Anticancer Res*, 22, 1727-30.
- ABDUL, M., RAMLAL, S. & HOOSEIN, N. 2008. Ryanodine receptor expression correlates with tumor grade in breast cancer. *Pathol Oncol Res*, 14, 157-60.
- ABDUL, M., SANTO, A. & HOOSEIN, N. 2003. Activity of potassium channel-blockers in breast cancer. *Anticancer Res*, 23, 3347-51.
- AKAMATSU, K., SHIBATA, M. A., ITO, Y., SOHMA, Y., AZUMA, H. & OTSUKI, Y. 2009. Riluzole induces apoptotic cell death in human prostate cancer cells via endoplasmic reticulum stress. *Anticancer Res*, 29, 2195-204.
- ALHOTHALI, M., MATHEW, M., IYER, G., LAWRENCE, H. R., YANG, S., CHELLAPPAN, S. & PADMANABHAN, J. 2019. Fendiline Enhances the Cytotoxic Effects of Therapeutic Agents on PDAC Cells by Inhibiting Tumor-Promoting Signaling Events: A Potential Strategy to Combat PDAC. *International journal of molecular sciences*, 20, 2423.
- ANDERSON, J. D., HANSEN, T. P., LENKOWSKI, P. W., WALLS, A. M., CHOUDHURY, I. M., SCHENCK, H. A., FRIEHLING, M., HOLL, G. M., PATEL, M. K., SIKES, R. A. & BROWN, M. L. 2003. Voltage-gated sodium channel blockers as cytostatic inhibitors of the androgen-independent prostate cancer cell line PC-3. *Mol Cancer Ther*, 2, 1149-54.
- ANGELUCCI, A., VALENTINI, A., MILLIMAGGI, D., GRAVINA, G. L., MIANO, R., DOLO, V., VICENTINI, C., BOLOGNA, M., FEDERICI, G. & BERNARDINI, S. 2006. Valproic

- acid induces apoptosis in prostate carcinoma cell lines by activation of multiple death pathways. *Anti-Cancer Drugs*, 17, 1141-1150.
- ARCANGELI, A. 2005. Expression and role of hERG channels in cancer cells. *Novartis Found Symp*, 266, 225-32; discussion 232-4.
- ARCANGELI, A. & BECCHETTI, A. 2006. Complex functional interaction between integrin receptors and ion channels. *Trends Cell Biol*, 16, 631-9.
- ARCANGELI, A., CROCIANI, O., LASTRAIOLI, E., MASI, A., PILLOZZI, S. & BECCHETTI, A. 2009. Targeting ion channels in cancer: a novel frontier in antineoplastic therapy. *Curr Med Chem*, 16, 66-93.
- ARIMOCHI, H. & MORITA, K. 2006. Characterization of cytotoxic actions of tricyclic antidepressants on human HT29 colon carcinoma cells. *Eur J Pharmacol*, 541, 17-23.
- ARIMOCHI, H. & MORITA, K. 2008. Desipramine induces apoptotic cell death through nonmitochondrial and mitochondrial pathways in different types of human colon carcinoma cells. *Pharmacology*, 81, 164-72.
- ARTYM, V. V. & PETTY, H. R. 2002. Molecular proximity of Kv1.3 voltage-gated potassium channels and β 1 -integrins on the plasma membrane of melanoma cells: Effects of cell adherence and channel blockers. *Journal of General Physiology*, 120, 29-37.
- ASHER, V., WARREN, A., SHAW, R., SOWTER, H., BALI, A. & KHAN, R. 2011. The role of Eag and HERG channels in cell proliferation and apoptotic cell death in SK-OV-3 ovarian cancer cell line. *Cancer Cell International*, 11, 6.
- BABAER, D., AMARA, S., IVY, M., ZHAO, Y., LAMMERS, P. E., TITZE, J. M. & TIRIVEEDHI, V. 2018. High salt induces P-glycoprotein mediated treatment resistance in breast cancer cells through store operated calcium influx. *Oncotarget*, 9, 25193-25205.
- BAO, X. X., XIE, B. S., LI, Q., LI, X. P., WEI, L. H. & WANG, J. L. 2012. Nifedipine induced autophagy through Beclin1 and mTOR pathway in endometrial carcinoma cells. *Chin Med J (Engl)*, 125, 3120-6.
- BAPTISTA-HON, D. T., ROBERTSON, F. M., ROBERTSON, G. B., OWEN, S. J., ROGERS, G. W., LYDON, E. L., LEE, N. H. & HALES, T. G. 2014. Potent inhibition by ropivacaine of metastatic colon cancer SW620 cell invasion and NaV1.5 channel function. *Br J Anaesth*, 113 Suppl 1, i39-i48.
- BATCIOGLU, K., UYUMLU, A. B., SATILMIS, B., YILDIRIM, B., YUCEL, N., DEMIRTAS, H., ONKAL, R., GUZEL, R. M. & DJAMGOZ, M. B. 2012. Oxidative Stress in the in vivo DMBA Rat Model of Breast Cancer: Suppression by a Voltage-gated Sodium Channel Inhibitor (RS100642). *Basic Clin Pharmacol Toxicol*, 111, 137-41.
- BAUDINO, T. A. 2015. Targeted Cancer Therapy: The Next Generation of Cancer Treatment. *Curr Drug Discov Technol*, 12, 3-20.
- BECCHETTI, A. 2011. Ion channels and transporters in cancer. 1. Ion channels and cell proliferation in cancer. *Am J Physiol Cell Physiol*, 301, C255-65.
- BENAVIDES-SERRATO, A., SAUNDERS, J. T., HOLMES, B., NISHIMURA, R. N., LICHTENSTEIN, A. & GERA, J. 2020. Repurposing Potential of Riluzole as an ITAF Inhibitor in mTOR Therapy Resistant Glioblastoma. *International journal of molecular sciences*, 21, 344.
- BERNAL-RAMOS, G., HERNANDEZ-GALLEGOS, E., VERA, E., CHAVEZ-LOPEZ, M. G., ZUNIGA-GARCIA, V., SANCHEZ-PEREZ, Y., GARRIDO, E. & CAMACHO, J. 2017. Astemizole inhibits cell proliferation in human prostate tumorigenic cells expressing ether a-go-go-1 potassium channels. *Cell Mol Biol (Noisy-le-grand)*, 63, 11-13.
- BERTOLESI, G. E., SHI, C., ELBAUM, L., JOLLMORE, C., ROZENBERG, G., BARNES, S. & KELLY, M. E. 2002. The Ca(2+) channel antagonists mibefradil and pimozide inhibit cell growth via different cytotoxic mechanisms. *Mol Pharmacol*, 62, 210-9.
- BERZINGI, S., NEWMAN, M. & YU, H.-G. 2016. Altering bioelectricity on inhibition of human breast cancer cells. *Cancer cell international*, 16, 72-72.
- BESSON, P., DRIFFORT, V., BON, E., GRADEK, F., CHEVALIER, S. & ROGER, S. 2015. How do voltage-gated sodium channels enhance migration and invasiveness in cancer cells? *Biochim Biophys Acta*, 1848, 2493-501.

- BHOURI, W., BOUBAKER, J., SKANDRANI, I., GHEDIRA, K. & CHEKIR GHEDIRA, L. 2012. Investigation of the apoptotic way induced by digallic acid in human lymphoblastoid TK6 cells. *Cancer cell international*, 12, 26-26.
- BIANCHI, L., WIBLE, B., ARCANGELI, A., TAGLIALATELA, M., MORRA, F., CASTALDO, P., CROCIANI, O., ROSATI, B., FARAVELLI, L., OLIVOTTO, M. & WANKE, E. 1998. hERG encodes a K⁺ current highly conserved in tumors of different histogenesis: a selective advantage for cancer cells? *Cancer Res*, 58, 815-22.
- BIBER, A., DURUSU, İ. Z. & ÖZEN, C. 2018. In vitro anticancer effect of tricyclic antidepressant nortriptyline on multiple myeloma. *Turkish journal of biology = Turk biyoloji dergisi*, 42, 414-421.
- BIDAUX, G., FLOURAKIS, M., THEBAULT, S., ZHOLOS, A., BECK, B., GKIKI, D., ROUDBARAKI, M., BONNAL, J. L., MAUROY, B., SHUBA, Y., SKRYMA, R. & PREVARSKAYA, N. 2007. Prostate cell differentiation status determines transient receptor potential melastatin member 8 channel subcellular localization and function. *J Clin Invest*, 117, 1647-57.
- BIKI, B., MASCHA, E., MORIARTY, D. C., FITZPATRICK, J. M., SESSLER, D. I. & BUGGY, D. J. 2008. Anesthetic technique for radical prostatectomy surgery affects cancer recurrence: a retrospective analysis. *Anesthesiology*, 109, 180-7.
- BILL, A., HALL, M. L., BORAWSKI, J., HODGSON, C., JENKINS, J., PIECHON, P., POPA, O., ROTHWELL, C., TRANTER, P., TRIA, S., WAGNER, T., WHITEHEAD, L. & GAITHER, L. A. 2014. Small molecule-facilitated degradation of ANO1 protein: a new targeting approach for anticancer therapeutics. *The Journal of biological chemistry*, 289, 11029-11041.
- BLACKISTON, D. J., MCLAUGHLIN, K. A. & LEVIN, M. 2009. Bioelectric controls of cell proliferation: ion channels, membrane voltage and the cell cycle. *Cell Cycle*, 8, 3519-28.
- BOLANZ, K. A., HEDIGER, M. A. & LANDOWSKI, C. P. 2008. The role of TRPV6 in breast carcinogenesis. *Mol Cancer Ther*, 7, 271-9.
- BOMBEN, V. C. & SONTHEIMER, H. 2010. Disruption of transient receptor potential canonical channel 1 causes incomplete cytokinesis and slows the growth of human malignant gliomas. *Glia*, 58, 1145-1156.
- BOMBEN, V. C. & SONTHEIMER, H. W. 2008. Inhibition of transient receptor potential canonical channels impairs cytokinesis in human malignant gliomas. *Cell Prolif*, 41, 98-121.
- BONDARAVA, M., LI, T., ENDL, E. & WEHNER, F. 2009. alpha-ENaC is a functional element of the hypertonicity-induced cation channel in HepG2 cells and it mediates proliferation. *Pflugers Arch*, 458, 675-87.
- BONG, A. H. L. & MONTEITH, G. R. 2018. Calcium signaling and the therapeutic targeting of cancer cells. *Biochim Biophys Acta Mol Cell Res*, 1865, 1786-1794.
- BONITO, B., SAUTER, D. R., SCHWAB, A., DJAMGOZ, M. B. & NOVAK, I. 2016. KCa3.1 (IK) modulates pancreatic cancer cell migration, invasion and proliferation: anomalous effects on TRAM-34. *Pflugers Arch*, 468, 1865-1875.
- BORRELLI, F., PAGANO, E., ROMANO, B., PANZERA, S., MAIELLO, F., COPPOLA, D., DE PETROCELLIS, L., BUONO, L., ORLANDO, P. & IZZO, A. A. 2014. Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychotropic cannabinoid. *Carcinogenesis*, 35, 2787-97.
- BOWEN, C. V., DEBAY, D., EWART, H. S., GALLANT, P., GORMLEY, S., ILENCHUK, T. T., IQBAL, U., LUTES, T., MARTINA, M., MEALING, G., MERKLEY, N., SPERKER, S., MORENO, M. J., RICE, C., SYVITSKI, R. T. & STEWART, J. M. 2013. In vivo detection of human TRPV6-rich tumors with anti-cancer peptides derived from soricidin. *PloS one*, 8, e58866-e58866.
- BRACKENBURY, W. J. 2016. Ion Channels in Cancer. In: PITT, G. S. (ed.) *Ion Channels in Health and Disease*. Elsevier Inc.

- BRACKENBURY, W. J., CHIONI, A. M., DISS, J. K. & DJAMGOZ, M. B. 2007. The neonatal splice variant of Nav1.5 potentiates in vitro invasive behaviour of MDA-MB-231 human breast cancer cells. *Breast Cancer Res Treat*, 101, 149-60.
- BRASKY, T. M., KROK-SCHOEN, J. L., LIU, J., CHLEBOWSKI, R. T., FREUDENHEIM, J. L., LAVASANI, S., MARGOLIS, K. L., QI, L., REDING, K. W., SHIELDS, P. G., SIMON, M. S., WACTAWSKI-WENDE, J., WANG, A., WOMACK, C. & MANSON, J. E. 2017. Use of Calcium Channel Blockers and Breast Cancer Risk in the Women's Health Initiative. *Cancer Epidemiol Biomarkers Prev*, 26, 1345-1348.
- BRISSON, L., GILLET, L., CALAGHAN, S., BESSON, P., LE GUENNEC, J. Y., ROGER, S. & GORE, J. 2011. Na(V)1.5 enhances breast cancer cell invasiveness by increasing NHE1-dependent H(+) efflux in caveolae. *Oncogene*, 30, 2070-6.
- BRITSCHGI, A., BILL, A., BRINKHAUS, H., ROTHWELL, C., CLAY, I., DUSS, S., REBHAN, M., RAMAN, P., GUY, C. T., WETZEL, K., GEORGE, E., POPA, M. O., LILLEY, S., CHOUDHURY, H., GOSLING, M., WANG, L., FITZGERALD, S., BORAWSKI, J., BAFFOE, J., LABOW, M., GAITHER, L. A. & BENTIREN-ALJ, M. 2013. Calcium-activated chloride channel ANO1 promotes breast cancer progression by activating EGFR and CAMK signaling. *Proc Natl Acad Sci U S A*, 110, E1026-34.
- BROCKSCHMIDT, C., HIRNER, H., HUBER, N., EISMANN, T., HILLENBRAND, A., GIAMAS, G., RADUNSKY, B., AMMERPOHL, O., BOHM, B., HENNE-BRUNS, D., KALTHOFF, H., LEITHAUSER, F., TRAUZOLD, A. & KNIPPSCHILD, U. 2008. Anti-apoptotic and growth-stimulatory functions of CK1 delta and epsilon in ductal adenocarcinoma of the pancreas are inhibited by IC261 in vitro and in vivo. *Gut*, 57, 799-806.
- BUCHANAN, P. J. & MCCLOSKEY, K. D. 2016. CaV channels and cancer: canonical functions indicate benefits of repurposed drugs as cancer therapeutics. *Eur Biophys J*, 45, 621-633.
- BUGAN, I., KUCUK, S., KARAGOZ, Z., FRASER, S. P., KAYA, H., DODSON, A., FOSTER, C. S., ALTUN, S. & DJAMGOZ, M. B. A. 2019. Anti-metastatic effect of ranolazine in an in vivo rat model of prostate cancer, and expression of voltage-gated sodium channel protein in human prostate. *Prostate Cancer Prostatic Dis*, 22, 569-579.
- CAMPBELL, T. M., MAIN, M. J. & FITZGERALD, E. M. 2013. Functional expression of the voltage-gated Na(+)-channel Nav1.7 is necessary for EGF-mediated invasion in human non-small cell lung cancer cells. *J Cell Sci*, 126, 4939-49.
- CAMPIA, I., SALA, V., KOPECKA, J., LEO, C., MITRO, N., COSTAMAGNA, C., CARUSO, D., PESCARMONA, G., CREPALDI, T., GHIGO, D., BOSIA, A. & RIGANTI, C. 2012. Digoxin and ouabain induce the efflux of cholesterol via liver X receptor signalling and the synthesis of ATP in cardiomyocytes. *Biochem J*, 447, 301-11.
- CHANG, H.-T., CHOU, C.-T., YU, C.-C., TSAI, J.-Y., SUN, T.-K., LIANG, W.-Z., LIN, K.-L., TSENG, H.-W., KUO, C.-C., CHEN, F.-A., KUO, D.-H., PAN, C.-C., HO, C.-M., SHIEH, P. & JAN, C.-R. 2015. The mechanism of protriptyline-induced Ca2+ movement and non-Ca2+-triggered cell death in PC3 human prostate cancer cells. *Journal of Receptors and Signal Transduction*, 35, 429-434.
- CHANG, Y.-L., LIU, S.-T., WANG, Y.-W., LIN, W.-S. & HUANG, S.-M. 2018. Amiodarone promotes cancer cell death through elevated truncated SRSF3 and downregulation of miR-224. *Oncotarget*, 9, 13390-13406.
- CHANG, Y. C., LIU, C. L., CHEN, M. J., HSU, Y. W., CHEN, S. N., LIN, C. H., CHEN, C. M., YANG, F. M. & HU, M. C. 2014. Local anesthetics induce apoptosis in human breast tumor cells. *Anesth Analg*, 118, 116-24.
- CHAVEZ-LOPEZ, M. G., ZUNIGA-GARCIA, V., HERNANDEZ-GALLEGOS, E., VERA, E., CHASQUIZA-ANCHATUNA, C. A., VITERI-YANEZ, M., SANCHEZ-RAMOS, J., GARRIDO, E. & CAMACHO, J. 2017. The combination astemizole-gefitinib as a potential therapy for human lung cancer. *Onco Targets Ther*, 10, 5795-5803.
- CHEN, B., ZHANG, C., WANG, Z., CHEN, Y., XIE, H., LI, S., LIU, X., LIU, Z. & CHEN, P. 2019. Mechanistic insights into Nav1.7-dependent regulation of rat prostate cancer

- cell invasiveness revealed by toxin probes and proteomic analysis. *FEBS J*, 286, 2549-2561.
- CHEN, D., SONG, M., MOHAMAD, O. & YU, S. P. 2014. Inhibition of Na⁺/K⁺-ATPase induces hybrid cell death and enhanced sensitivity to chemotherapy in human glioblastoma cells. *BMC Cancer*, 14, 716.
- CHEN, Y., SÁNCHEZ, A., RUBIO, M. E., KOHL, T., PARDO, L. A. & STÜHMER, W. 2011. Functional K(v)10.1 channels localize to the inner nuclear membrane. *PloS one*, 6, e19257-e19257.
- CHENG, Y., GULBINS, E. & SIEMEN, D. 2011. Activation of the permeability transition pore by Bax via inhibition of the mitochondrial BK channel. *Cell Physiol Biochem*, 27, 191-200.
- CHERUBINI, A., HOFMANN, G., PILLOZZI, S., GUASTI, L., CROCIANI, O., CILIA, E., DI STEFANO, P., DEGANI, S., BALZI, M., OLIVOTTO, M., WANKE, E., BECCHETTI, A., DEFILIPPI, P., WYMORE, R. & ARCANGELI, A. 2005. Human ether-a-go-go-related gene 1 channels are physically linked to beta1 integrins and modulate adhesion-dependent signaling. *Mol Biol Cell*, 16, 2972-83.
- CHERUBINI, A., TADDEI, G. L., CROCIANI, O., PAGLIERANI, M., BUCCOLIERO, A. M., FONTANA, L., NOCI, I., BORRI, P., BORRANI, E., GIACHI, M., BECCHETTI, A., ROSATI, B., WANKE, E., OLIVOTTO, M. & ARCANGELI, A. 2000. HERG potassium channels are more frequently expressed in human endometrial cancer as compared to non-cancerous endometrium. *Br J Cancer*, 83, 1722-9.
- CHIANG, E. Y., LI, T., JEET, S., PENG, I., ZHANG, J., LEE, W. P., DEVOSS, J., CAPLAZI, P., CHEN, J., WARMING, S., HACKOS, D. H., MUKUND, S., KOTH, C. M. & GROGAN, J. L. 2017. Potassium channels Kv1.3 and KCa3.1 cooperatively and compensatorily regulate antigen-specific memory T cell functions. *Nature Communications*, 8, 14644.
- CHIONI, A. M., FRASER, S. P., PANI, F., FORAN, P., WILKIN, G. P., DISS, J. K. & DJAMGOZ, M. B. 2005. A novel polyclonal antibody specific for the Na(v)1.5 voltage-gated Na(+) channel 'neonatal' splice form. *J Neurosci Methods*, 147, 88-98.
- CHITTAJALLU, R., CHEN, Y., WANG, H., YUAN, X., GHIANI, C. A., HECKMAN, T., MCBAIN, C. J. & GALLO, V. 2002. Regulation of Kv1 subunit expression in oligodendrocyte progenitor cells and their role in G1/S phase progression of the cell cycle. *Proc Natl Acad Sci U S A*, 99, 2350-5.
- CLARE, J. J., TATE, S. N., NOBBS, M. & ROMANOS, M. A. 2000. Voltage-gated sodium channels as therapeutic targets. *Drug Discov Today*, 5, 506-520.
- CONRAD, D. M., FURLONG, S. J., DOUCETTE, C. D., WEST, K. A. & HOSKIN, D. W. 2010. The Ca(2+) channel blocker flunarizine induces caspase-10-dependent apoptosis in Jurkat T-leukemia cells. *Apoptosis*, 15, 597-607.
- CONTASSOT, E., TENAN, M., SCHNÜRIGER, V., PELTE, M. F. & DIETRICH, P. Y. 2004a. Arachidonyl ethanolamide induces apoptosis of uterine cervix cancer cells via aberrantly expressed vanilloid receptor-1. *Gynecol Oncol*, 93, 182-8.
- CONTASSOT, E., WILMOTTE, R., TENAN, M., BELKOUCH, M.-C., SCHNÜRIGER, V., DE TRIBOLET, N., BOURKHARDT, K. & DIETRICH, P.-Y. 2004b. Arachidonylethanolamide Induces Apoptosis of Human Glioma Cells through Vanilloid Receptor-1. *Journal of Neuropathology & Experimental Neurology*, 63, 956-963.
- CROCIANI, O., LASTRAIOLI, E., BONI, L., PILLOZZI, S., ROMOLI, M. R., D'AMICO, M., STEFANINI, M., CRESCIOLI, S., MASI, A., TADDEI, A., BENCINI, L., BERNINI, M., FARSI, M., BEGHELLI, S., SCARPA, A., MESSERINI, L., TOMEZZOLI, A., VINDIGNI, C., MORGAGNI, P., SARAGONI, L., GIOMMONI, E., GASPERONI, S., DI COSTANZO, F., ROVIELLO, F., DE MANZONI, G., BECHI, P. & ARCANGELI, A. 2014. hERG1 channels regulate VEGF-A secretion in human gastric cancer: clinicopathological correlations and therapeutical implications. *Clin Cancer Res*, 20, 1502-12.

- CROCIANI, O., ZANIERI, F., PILLOZZI, S., LASTRAIOLI, E., STEFANINI, M., FIORE, A., FORTUNATO, A., D'AMICO, M., MASSELLI, M., DE LORENZO, E., GASPAROLI, L., CHIU, M., BUSSOLATI, O., BECCHETTI, A. & ARCANGELI, A. 2013. hERG1 channels modulate integrin signaling to trigger angiogenesis and tumor progression in colorectal cancer. *Scientific Reports*, 3, 3308.
- DARVIN, P., BAEG, S. J., JOUNG, Y. H., SP, N., KANG, D. Y., BYUN, H. J., PARK, J. U. & YANG, Y. M. 2015. Tannic acid inhibits the Jak2/STAT3 pathway and induces G1/S arrest and mitochondrial apoptosis in YD-38 gingival cancer cells. *Int J Oncol*, 47, 1111-20.
- DE GUADALUPE CHAVEZ-LOPEZ, M., PEREZ-CARREON, J. I., ZUNIGA-GARCIA, V., DIAZ-CHAVEZ, J., HERRERA, L. A., CARO-SANCHEZ, C. H., ACUNA-MACIAS, I., GARIGLIO, P., HERNANDEZ-GALLEGOS, E., CHILQUINGA, A. J. & CAMACHO, J. 2015. Astemizole-based anticancer therapy for hepatocellular carcinoma (HCC), and Eag1 channels as potential early-stage markers of HCC. *Tumour Biol*, 36, 6149-58.
- DE MARCHI, U., SASSI, N., FIORETTI, B., CATACUZZENO, L., CEREGHETTI, G. M., SZABÓ, I. & ZORATTI, M. 2009. Intermediate conductance Ca²⁺-activated potassium channel (KCa3.1) in the inner mitochondrial membrane of human colon cancer cells. *Cell Calcium*, 45, 509-16.
- DE PETROCELLIS, L., MELCK, D., PALMISANO, A., BISOGNO, T., LAEZZA, C., BIFULCO, M. & DI MARZO, V. 1998. The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation. *Proceedings of the National Academy of Sciences of the United States of America*, 95, 8375-8380.
- DEL MONACO, S. M., MARINO, G. I., ASSEF, Y. A., DAMIANO, A. E. & KOTSIAS, B. A. 2009. Cell migration in BeWo cells and the role of epithelial sodium channels. *J Membr Biol*, 232, 1-13.
- DESHANE, J., GARNER, C. C. & SONTHEIMER, H. 2003. Chlorotoxin inhibits glioma cell invasion via matrix metalloproteinase-2. *J Biol Chem*, 278, 4135-44.
- DEVITA, V. T., JR. & CHU, E. 2008. A history of cancer chemotherapy. *Cancer Res*, 68, 8643-53.
- DING, X. W., LUO, H. S., JIN, X., YAN, J. J. & AI, Y. W. 2007. Aberrant expression of Eag1 potassium channels in gastric cancer patients and cell lines. *Med Oncol*, 24, 345-50.
- DJAMGOZ, M. B., COOMBES, R. C. & SCHWAB, A. 2014. Ion transport and cancer: from initiation to metastasis. *Philos Trans R Soc Lond B Biol Sci*, 369, 20130092.
- DJAMGOZ, M. B. & ONKAL, R. 2013. Persistent current blockers of voltage-gated sodium channels: a clinical opportunity for controlling metastatic disease. *Recent Pat Anticancer Drug Discov*, 8, 66-84.
- DJAMGOZ, M. B. A., FRASER, S. P. & BRACKENBURY, W. J. 2019. In Vivo Evidence for Voltage-Gated Sodium Channel Expression in Carcinomas and Potentiation of Metastasis. *Cancers (Basel)*, 11.
- DOLDERER, J. H., SCHULDES, H., BOCKHORN, H., ALTMANNBERGER, M., LAMBERS, C., VON ZABERN, D., JONAS, D., SCHWEGLER, H., LINKE, R. & SCHRÖDER, U. H. 2010. HERG1 gene expression as a specific tumor marker in colorectal tissues. *Eur J Surg Oncol*, 36, 72-7.
- DONG, Y., FURUTA, T., SABIT, H., KITABAYASHI, T., JIAPAER, S., KOBAYASHI, M., INO, Y., TODO, T., TENG, L., HIRAO, A., ZHAO, S.-G. & NAKADA, M. 2017. Identification of antipsychotic drug fluspirilene as a potential anti-glioma stem cell drug. *Oncotarget*, 8, 111728-111741.
- DRIFFORT, V., GILLET, L., BON, E., MARIONNEAU-LAMBOT, S., OULLIER, T., JOULIN, V., COLLIN, C., PAGES, J. C., JOURDAN, M. L., CHEVALIER, S., BOUGNOUX, P., LE GUENNEC, J. Y., BESSON, P. & ROGER, S. 2014. Ranolazine inhibits Nav1.5-mediated breast cancer cell invasiveness and lung colonization. *Mol Cancer*, 13, 264.
- DUBOIS, C., VANDEN ABELE, F., LEHEN'KYI, V., GKIKI, D., GUARMIT, B., LEPAGE, G., SLOMIANNY, C., BOROWIEC, A. S., BIDAUX, G., BENAHMED, M., SHUBA, Y. & PREVARSKAYA, N. 2014. Remodeling of channel-forming ORAI proteins determines an oncogenic switch in prostate cancer. *Cancer Cell*, 26, 19-32.

- DURANTI, C. & ARCANGELI, A. 2019. Ion Channel Targeting with Antibodies and Antibody Fragments for Cancer Diagnosis. *Antibodies (Basel)*, 8.
- DURANTI, C., CARRARESI, L., SETTE, A., STEFANINI, M., LOTTINI, T., CRESCIOLI, S., CROCIANI, O., IAMELE, L., DE JONGE, H., GHERARDI, E. & ARCANGELI, A. 2018. Generation and characterization of novel recombinant anti-hERG1 scFv antibodies for cancer molecular imaging. *Oncotarget*, 9, 34972-34989.
- DUTTA, S., LOPEZ CHARCAS, O., TANNER, S., GRADEK, F., DRIFFORT, V., ROGER, S., SELANDER, K., VELU, S. E. & BROUILLETTE, W. 2018. Discovery and evaluation of nNav1.5 sodium channel blockers with potent cell invasion inhibitory activity in breast cancer cells. *Bioorg Med Chem*, 26, 2428-2436.
- DZIEGIELEWSKA, B., BRAUTIGAN, D. L., LARNER, J. M. & DZIEGIELEWSKI, J. 2014. T-type Ca^{2+} channel inhibition induces p53-dependent cell growth arrest and apoptosis through activation of p38-MAPK in colon cancer cells. *Mol Cancer Res*, 12, 348-58.
- EIL, R., VODNALA, S. K., CLEVER, D., KLEBANOFF, C. A., SUKUMAR, M., PAN, J. H., PALMER, D. C., GROS, A., YAMAMOTO, T. N., PATEL, S. J., GUITTARD, G. C., YU, Z., CARBONARO, V., OKKENHAUG, K., SCHRUMP, D. S., LINEHAN, W. M., ROYCHOUDHURI, R. & RESTIFO, N. P. 2016. Ionic immune suppression within the tumour microenvironment limits T cell effector function. *Nature*, 537, 539-543.
- ELLIOTT, M. J., JERZAK, K. J., COCKBURN, J. G., SAFIKHANI, Z., GWYNNE, W. D., HASSELL, J. A., BANE, A., SILVESTER, J., THU, K. L., HAIBE-KAINS, B., MAK, T. W. & CESCONE, D. W. 2018. The Antiarrhythmic Drug, Dronedronone, Demonstrates Cytotoxic Effects in Breast Cancer Independent of Thyroid Hormone Receptor Alpha 1 (THRalpha1) Antagonism. *Sci Rep*, 8, 16562.
- EXADAKTYLOS, A. K., BUGGY, D. J., MORIARTY, D. C., MASCHA, E. & SESSLER, D. I. 2006. Can anesthetic technique for primary breast cancer surgery affect recurrence or metastasis? *Anesthesiology*, 105, 660-4.
- FAIRHURST, C., MARTIN, F., WATT, I., DORAN, T., BLAND, M. & BRACKENBURY, W. J. 2016. Sodium channel-inhibiting drugs and cancer survival: protocol for a cohort study using the CPRD primary care database. *BMJ Open*, 6, e011661.
- FAIRHURST, C., WATT, I., MARTIN, F., BLAND, M. & BRACKENBURY, W. J. 2014. Exposure to sodium channel-inhibiting drugs and cancer survival: protocol for a cohort study using the QResearch primary care database. *BMJ Open*, 4, e006604.
- FAIRHURST, C., WATT, I., MARTIN, F., BLAND, M. & BRACKENBURY, W. J. 2015. Sodium channel-inhibiting drugs and survival of breast, colon and prostate cancer: a population-based study. *Sci Rep*, 5, 16758.
- FELIPPE GONCALVES-DE-ALBUQUERQUE, C., RIBEIRO SILVA, A., IGNACIO DA SILVA, C., CAIRE CASTRO-FARIA-NETO, H. & BURTH, P. 2017. Na/K Pump and Beyond: Na/K-ATPase as a Modulator of Apoptosis and Autophagy. *Molecules*, 22.
- FERNÁNDEZ-SALAS, E., SUH, K. S., SPERANSKY, V. V., BOWERS, W. L., LEVY, J. M., ADAMS, T., PATHAK, K. R., EDWARDS, L. E., HAYES, D. D., CHENG, C., STEVEN, A. C., WEINBERG, W. C. & YUSPA, S. H. 2002. mtCLIC/CLIC4, an organellar chloride channel protein, is increased by DNA damage and participates in the apoptotic response to p53. *Mol Cell Biol*, 22, 3610-20.
- FIORIO PLA, A., AVANZATO, D., MUNARON, L. & AMBUDKAR, I. S. 2012. Ion channels and transporters in cancer. 6. Vascularizing the tumor: TRP channels as molecular targets. *Am J Physiol Cell Physiol*, 302, C9-15.
- FÖHR, K., KNIPPSCHILD, U., HERKOMMER, A., FAULER, M., PEIFER, C., GEORGIEFF, M. & ADOLPH, O. 2017. State-dependent block of voltage-gated sodium channels by the casein-kinase 1 inhibitor IC261. *Investigational New Drugs*, 35, 277-289.
- FRASER, S. P., DISS, J. K., CHIONI, A. M., MYCIELSKA, M. E., PAN, H., YAMACI, R. F., PANI, F., SIWY, Z., KRASOWSKA, M., GRZYWNA, Z., BRACKENBURY, W. J., THEODOROU, D., KOYUTURK, M., KAYA, H., BATTALOGLU, E., DE BELLA, M. T., SLADE, M. J., TOLHURST, R., PALMIERI, C., JIANG, J., LATCHMAN, D. S., COOMBES, R. C. & DJAMGOZ, M. B. 2005. Voltage-gated sodium channel

- expression and potentiation of human breast cancer metastasis. *Clin Cancer Res*, 11, 5381-9.
- FRASER, S. P., GRIMES, J. A., DISS, J. K., STEWART, D., DOLLY, J. O. & DJAMGOZ, M. B. 2003a. Predominant expression of Kv1.3 voltage-gated K⁺ channel subunit in rat prostate cancer cell lines: electrophysiological, pharmacological and molecular characterisation. *Pflugers Arch*, 446, 559-71.
- FRASER, S. P., GRIMES, J. A. & DJAMGOZ, M. B. 2000. Effects of voltage-gated ion channel modulators on rat prostatic cancer cell proliferation: comparison of strongly and weakly metastatic cell lines. *Prostate*, 44, 61-76.
- FRASER, S. P., SALVADOR, V., MANNING, E. A., MIZAL, J., ALTUN, S., RAZA, M., BERRIDGE, R. J. & DJAMGOZ, M. B. 2003b. Contribution of functional voltage-gated Na⁺ channel expression to cell behaviors involved in the metastatic cascade in rat prostate cancer: I. Lateral motility. *J Cell Physiol*, 195, 479-87.
- FU, S., HIRTE, H., WELCH, S., ILENCHUK, T. T., LUTES, T., RICE, C., FIELDS, N., NEMET, A., DUGOURD, D., PIHA-PAUL, S., SUBBIAH, V., LIU, L., GONG, J., HONG, D. & STEWART, J. M. 2017. First-in-human phase I study of SOR-C13, a TRPV6 calcium channel inhibitor, in patients with advanced solid tumors. *Invest New Drugs*, 35, 324-333.
- FUCA, G., GALLI, G., POGGI, M., LO RUSSO, G., PROTO, C., IMBIMBO, M., VITALI, M., GANZINELLI, M., LANTI, C., MOLINO, G., STANGONI, F., ZILEMBO, N., DE BRAUD, F., GARASSINO, M. C. & SIGNORELLI, D. 2018. Low Baseline Serum Sodium Concentration Is Associated with Poor Clinical Outcomes in Metastatic Non-Small Cell Lung Cancer Patients Treated with Immunotherapy. *Target Oncol*, 13, 795-800.
- GACKIERE, F., BIDAUX, G., DELCOURT, P., VAN COPPENOLLE, F., KATSOGIANNOU, M., DEWAILLY, E., BAVENCOFFE, A., VAN CHUOI-MARIOT, M. T., MAUROY, B., PREVARSKAYA, N. & MARIOT, P. 2008. CaV3.2 T-type calcium channels are involved in calcium-dependent secretion of neuroendocrine prostate cancer cells. *J Biol Chem*, 283, 10162-73.
- GARCIA-FERREIRO, R. E., KERSCHENSTEINER, D., MAJOR, F., MONJE, F., STUHMER, W. & PARDO, L. A. 2004. Mechanism of block of hEag1 K⁺ channels by imipramine and astemizole. *J Gen Physiol*, 124, 301-17.
- GARCIA-QUIROZ, J. & CAMACHO, J. 2011. Astemizole: an old anti-histamine as a new promising anti-cancer drug. *Anticancer Agents Med Chem*, 11, 307-14.
- GARCÍA-QUIROZ, J., GARCÍA-BECERRA, R., BARRERA, D., SANTOS, N., AVILA, E., ORDAZ-ROSADO, D., RIVAS-SUÁREZ, M., HALHALI, A., RODRÍGUEZ, P., GAMBOA-DOMÍNGUEZ, A., MEDINA-FRANCO, H., CAMACHO, J., LARREA, F. & DÍAZ, L. 2012. Astemizole synergizes calcitriol antiproliferative activity by inhibiting CYP24A1 and upregulating VDR: a novel approach for breast cancer therapy. *PLoS one*, 7, e45063-e45063.
- GARCÍA-QUIROZ, J., GARCÍA-BECERRA, R., SANTOS-MARTÍNEZ, N., BARRERA, D., ORDAZ-ROSADO, D., AVILA, E., HALHALI, A., VILLANUEVA, O., IBARRA-SÁNCHEZ, M. J., ESPARZA-LÓPEZ, J., GAMBOA-DOMÍNGUEZ, A., CAMACHO, J., LARREA, F. & DÍAZ, L. 2014. In vivo dual targeting of the oncogenic Ether-à-go-go-1 potassium channel by calcitriol and astemizole results in enhanced antineoplastic effects in breast tumors. *BMC cancer*, 14, 745-745.
- GARZON-MUVDI, T., SCHIAPPARELLI, P., AP RHYS, C., GUERRERO-CAZARES, H., SMITH, C., KIM, D. H., KONE, L., FARBER, H., LEE, D. Y., AN, S. S., LEVCHENKO, A. & QUINONES-HINOJOSA, A. 2012. Regulation of brain tumor dispersal by NKCC1 through a novel role in focal adhesion regulation. *PLoS Biol*, 10, e1001320.
- GAUTIER, M., TREBAK, M., FLEIG, A., VANDIER, C. & OUADID-AHIDOUCH, H. 2019. Ca(2+) channels in cancer. *Cell Calcium*, 84, 102083.
- GAVRILOVA-RUCH, O., SCHÖNHERR, K., GESSNER, G., SCHÖNHERR, R., KLAPPERSTÜCK, T., WOHLRAB, W. & HEINEMANN, S. H. 2002. Effects of

- imipramine on ion channels and proliferation of IGR1 melanoma cells. *J Membr Biol*, 188, 137-49.
- GENOVA, T., GROLEZ, G. P., CAMILLO, C., BERNARDINI, M., BOKHOBZA, A., RICHARD, E., SCIANNA, M., LEMONNIER, L., VALDEMBRI, D., MUNARON, L., PHILIPS, M. R., MATTOT, V., SERINI, G., PREVARSKAYA, N., GKIKA, D. & PLA, A. F. 2017. TRPM8 inhibits endothelial cell migration via a non-channel function by trapping the small GTPase Rap1. *J Cell Biol*, 216, 2107-2130.
- GEORGE, A. L., JR. 2005. Inherited disorders of voltage-gated sodium channels. *J Clin Invest*, 115, 1990-9.
- GILBERT, S. M., GIDLEY BAIRD, A., GLAZER, S., BARDEN, J. A., GLAZER, A., TEH, L. C. & KING, J. 2017. A phase I clinical trial demonstrates that nfP2X7 -targeted antibodies provide a novel, safe and tolerable topical therapy for basal cell carcinoma. *Br J Dermatol*, 177, 117-124.
- GILBERT, S. M., OLIPHANT, C. J., HASSAN, S., PEILLE, A. L., BRONSERT, P., FALZONI, S., DI VIRGILIO, F., MCNULTY, S. & LARA, R. 2019. ATP in the tumour microenvironment drives expression of nfP2X7, a key mediator of cancer cell survival. *Oncogene*, 38, 194-208.
- GILLET, L., ROGER, S., BESSON, P., LECAILLE, F., GORE, J., BOUGNOUX, P., LALMANACH, G. & LE GUENNEC, J. Y. 2009. Voltage-gated Sodium Channel Activity Promotes Cysteine Cathepsin-dependent Invasiveness and Colony Growth of Human Cancer Cells. *J Biol Chem*, 284, 8680-91.
- GILLET, L., ROGER, S., BOUGNOUX, P., LE GUENNEC, J. Y. & BESSON, P. 2011. Beneficial effects of omega-3 long-chain fatty acids in breast cancer and cardiovascular diseases: voltage-gated sodium channels as a common feature? *Biochimie*, 93, 4-6.
- GÓMEZ-VARELA, D., ZWICK-WALLASCH, E., KNÖTGEN, H., SÁNCHEZ, A., HETTMANN, T., OSSIOV, D., WESELOH, R., CONTRERAS-JURADO, C., ROTHE, M., STÜHMER, W. & PARDO, L. A. 2007. Monoclonal antibody blockade of the human Eag1 potassium channel function exerts antitumor activity. *Cancer research*, 67, 7343-7349.
- GOULD, H. J., 3RD, NORLEANS, J., WARD, T. D., REID, C. & PAUL, D. 2018. Selective lysis of breast carcinomas by simultaneous stimulation of sodium channels and blockade of sodium pumps. *Oncotarget*, 9, 15606-15615.
- GRIMALDI, C., PISANTI, S., LAEZZA, C., MALFITANO, A. M., SANTORO, A., VITALE, M., CARUSO, M. G., NOTARNICOLA, M., IACUZZO, I., PORTELLA, G., DI MARZO, V. & BIFULCO, M. 2006. Anandamide inhibits adhesion and migration of breast cancer cells. *Exp Cell Res*, 312, 363-73.
- GRIMALDI-BENSOUDA, L., KLUNGEL, O., KURZ, X., DE GROOT, M. C. H., MACIEL AFONSO, A. S., DE BRUIN, M. L., REYNOLDS, R. & ROSSIGNOL, M. 2016. Calcium channel blockers and cancer: a risk analysis using the UK Clinical Practice Research Datalink (CPRD). *BMJ Open*, 6.
- GRIMES, J. A. & DJAMGOZ, M. B. A. 1998. Electrophysiological characterization of voltage-gated Na⁺ current expressed in the highly metastatic Mat-LyLu cell line of rat prostate cancer. *Journal of Cellular Physiology*, 175, 50-58.
- GRIMES, J. A., FRASER, S. P., STEPHENS, G. J., DOWNING, J. E., LANIADO, M. E., FOSTER, C. S., ABEL, P. D. & DJAMGOZ, M. B. 1995. Differential expression of voltage-activated Na⁺ currents in two prostatic tumour cell lines: contribution to invasiveness in vitro. *FEBS Lett*, 369, 290-4.
- GROLEZ, G. P., HAMMADI, M., BARRAS, A., GORDIENKO, D., SLOMIANNY, C., VOLKEL, P., ANGRAND, P. O., PINAULT, M., GUIMARAES, C., POTIER-CARTEREAU, M., PREVARSKAYA, N., BOUKHERROUB, R. & GKIKA, D. 2019. Encapsulation of a TRPM8 Agonist, WS12, in Lipid Nanocapsules Potentiates PC3 Prostate Cancer Cell Migration Inhibition through Channel Activation. *Sci Rep*, 9, 7926.

- GUAN, L., SONG, Y., GAO, J., GAO, J. & WANG, K. 2016. Inhibition of calcium-activated chloride channel ANO1 suppresses proliferation and induces apoptosis of epithelium originated cancer cells. *Oncotarget*, 7, 78619-78630.
- GUILBERT, A., GAUTIER, M., DHENNIN-DUTHILLE, I., HAREN, N., SEVESTRE, H. & OUADID-AHIDOUCH, H. 2009. Evidence that TRPM7 is required for breast cancer cell proliferation. *Am J Physiol Cell Physiol*, 297, C493-502.
- GURURAJA RAO, S., PATEL, N. J. & SINGH, H. 2020. Intracellular Chloride Channels: Novel Biomarkers in Diseases. *Frontiers in physiology*, 11, 96-96.
- GUZEL, R. M., OGMEN, K., ILIEVA, K. M., FRASER, S. P. & DJAMGOZ, M. B. A. 2019. Colorectal cancer invasiveness in vitro: Predominant contribution of neonatal Nav1.5 under normoxia and hypoxia. *J Cell Physiol*, 234, 6582-6593.
- HAAS, B. R. & SONTHEIMER, H. 2010. Inhibition of the Sodium-Potassium-Chloride Cotransporter Isoform-1 reduces glioma invasion. *Cancer Res*, 70, 5597-606.
- HAAS, M., WANG, H., TIAN, J. & XIE, Z. 2002. Src-mediated inter-receptor cross-talk between the Na⁺/K⁺-ATPase and the epidermal growth factor receptor relays the signal from ouabain to mitogen-activated protein kinases. *J Biol Chem*, 277, 18694-702.
- HABELA, C. W., ERNEST, N. J., SWINDALL, A. F. & SONTHEIMER, H. 2009. Chloride accumulation drives volume dynamics underlying cell proliferation and migration. *J Neurophysiol*, 101, 750-7.
- HABELA, C. W., OLSEN, M. L. & SONTHEIMER, H. 2008. CIC3 is a critical regulator of the cell cycle in normal and malignant glial cells. *J Neurosci*, 28, 9205-17.
- HAMTIAUX, L., HANSOULLE, L., DAUGUET, N., MUCCIOLI, G. G., GALLEZ, B. & LAMBERT, D. M. 2011. Increasing antiproliferative properties of endocannabinoids in N1E-115 neuroblastoma cells through inhibition of their metabolism. *PLoS One*, 6, e26823.
- HAN, X., WANG, F., YAO, W., XING, H., WENG, D., SONG, X., CHEN, G., XI, L., ZHU, T., ZHOU, J., XU, G., WANG, S., MENG, L., IADECOLA, C., WANG, G. & MA, D. 2007. Heat shock proteins and p53 play a critical role in K⁺ channel-mediated tumor cell proliferation and apoptosis. *Apoptosis*, 12, 1837-46.
- HARTUNG, F., STÜHMER, W. & PARDO, L. 2011. Tumor cell-selective apoptosis induction through targeting of KV 10.1 via bifunctional TRAIL antibody. *Molecular Cancer*, 10, 109.
- HAUX, J., KLEPP, O., SPIGSET, O. & TRETLI, S. 2001. Digitoxin medication and cancer; case control and internal dose-response studies. *BMC Cancer*, 1, 11.
- HE, M., LIU, S., GALLOLU KANKANAMALAGE, S., BORROMEO, M. D., GIRARD, L., GAZDAR, A. F., MINNA, J. D., JOHNSON, J. E. & COBB, M. H. 2018. The Epithelial Sodium Channel (αENaC) Is a Downstream Therapeutic Target of ASCL1 in Pulmonary Neuroendocrine Tumors. *Translational Oncology*, 11, 292-299.
- HEGLE, A. P., MARBLE, D. D. & WILSON, G. F. 2006. A voltage-driven switch for ion-independent signaling by ether-a-go-go K⁺ channels. *Proc Natl Acad Sci U S A*, 103, 2886-91.
- HOLDHOFF, M., YE, X., SUPKO, J. G., NABORS, L. B., DESAI, A. S., WALBERT, T., LESSER, G. J., READ, W. L., LIEBERMAN, F. S., LODGE, M. A., LEAL, J., FISHER, J. D., DESIDERI, S., GROSSMAN, S. A., WAHL, R. L. & SCHIFF, D. 2017. Timed sequential therapy of the selective T-type calcium channel blocker mibefradil and temozolomide in patients with recurrent high-grade gliomas. *Neuro Oncol*, 19, 845-852.
- HONG, S., BI, M., WANG, L., KANG, Z., LING, L. & ZHAO, C. 2015. CLC-3 channels in cancer (review). *Oncol Rep*, 33, 507-14.
- HONN, K. V., ONODA, J. M., DIGLIO, C. A., CARUFEL, M. M., TAYLOR, J. D. & SLOANE, B. F. 1984. Inhibition of tumor cell-platelet interactions and tumor metastasis by the calcium channel blocker, nimodipine. *Clin Exp Metastasis*, 2, 61-72.
- HONN, K. V., ONODA, J. M., PAMPALONA, K., BATTAGLIA, M., NEAGOS, G., TAYLOR, J. D., DIGLIO, C. A. & SLOANE, B. F. 1985. Inhibition by dihydropyridine class calcium

- channel blockers of tumor cell-platelet-endothelial cell interactions in vitro and metastasis in vivo. *Biochem Pharmacol*, 34, 235-41.
- HOPKINS, M. M., FENG, X., LIU, M., PARKER, L. P. & KOH, D. W. 2015. Inhibition of the transient receptor potential melastatin-2 channel causes increased DNA damage and decreased proliferation in breast adenocarcinoma cells. *Int J Oncol*, 46, 2267-76.
- HUANG, J., FURUYA, H., FAOUZI, M., ZHANG, Z., MONTEILH-ZOLLER, M., KELLY GALBRAITH KAWABATA, F., HORGAN, D., KAWAMORI, T., PENNER, R. & FLEIG, A. 2017. Inhibition of TRPM7 suppresses cell proliferation of colon adenocarcinoma in vitro and induces hypomagnesemia in vivo without affecting azoxymethane-induced early colon cancer in mice. *Cell Communication and Signaling*, 15, <xocs:firstpage xmlns:xocs=""/>.
- HUANG, W., LU, C., WU, Y., OUYANG, S. & CHEN, Y. 2015. T-type calcium channel antagonists, mibefradil and NNC-55-0396 inhibit cell proliferation and induce cell apoptosis in leukemia cell lines. *Journal of experimental & clinical cancer research : CR*, 34, 54-54.
- HUANG, X. & JAN, L. Y. 2014. Targeting potassium channels in cancer. *J Cell Biol*, 206, 151-62.
- HUMEAU, J., BRAVO-SAN PEDRO, J. M., VITALE, I., NUÑEZ, L., VILLALOBOS, C., KROEMER, G. & SENOVILLA, L. 2018. Calcium signaling and cell cycle: Progression or death. *Cell Calcium*, 70, 3-15.
- HUTCHINGS, C. J., COLUSSI, P. & CLARK, T. 2019. Ion channels as therapeutic antibody targets. *mAbs*.
- ILLEK, B., FISCHER, H. & MACHEN, T. E. 1992. Intracellular Ca²⁺ signalling is modulated by K⁺ channel blockers in colonic epithelial cells (HT-29/B6). *Pflugers Arch*, 422, 48-54.
- INNAMAA, A., JACKSON, L., ASHER, V., VAN SHALKWYK, G., WARREN, A., HAY, D., BALI, A., SOWTER, H. & KHAN, R. 2013. Expression and prognostic significance of the oncogenic K2P potassium channel KCNK9 (TASK-3) in ovarian carcinoma. *Anticancer Res*, 33, 1401-8.
- ISBILEN, B., FRASER, S. P. & DJAMGOZ, M. B. 2006. Docosahexaenoic acid (omega-3) blocks voltage-gated sodium channel activity and migration of MDA-MB-231 human breast cancer cells. *Int J Biochem Cell Biol*, 38, 2173-82.
- JANG, S. H., BYUN, J. K., JEON, W. I., CHOI, S. Y., PARK, J., LEE, B. H., YANG, J. E., PARK, J. B., O'GRADY, S. M., KIM, D. Y., RYU, P. D., JOO, S. W. & LEE, S. Y. 2015. Nuclear localization and functional characteristics of voltage-gated potassium channel Kv1.3. *J Biol Chem*, 290, 12547-57.
- JANG, S. J., CHOI, H. W., CHOI, D. L., CHO, S., RIM, H. K., CHOI, H. E., KIM, K. S., HUANG, M., RHIM, H., LEE, K. T. & LEE, J. Y. 2013. In vitro cytotoxicity on human ovarian cancer cells by T-type calcium channel blockers. *Bioorg Med Chem Lett*, 23, 6656-62.
- JOSE, C., HEBERT-CHATELAIN, E., DIAS AMOEDO, N., ROCHE, E., OBRE, E., LACOMBE, D., REZVANI, H. R., POURQUIER, P., NOUETTE-GAULAIN, K. & ROSSIGNOL, R. 2018. Redox mechanism of levobupivacaine cytostatic effect on human prostate cancer cells. *Redox Biology*, 18, 33-42.
- KADDOUR-DJEBBAR, I., CHOUDHARY, V., LAKSHMIKANTHAN, V., SHIRLEY, R., EL GAISH, M., AL-SHABRAWAY, M., AL-HUSEIN, B., ZHONG, R., DAVIS, M., DONG, Z., BOLLAG, W. B. & KUMAR, M. V. 2012. Diltiazem enhances the apoptotic effects of proteasome inhibitors to induce prostate cancer cell death. *J Pharmacol Exp Ther*, 341, 646-55.
- KANG, H. B., RIM, H. K., PARK, J. Y., CHOI, H. W., CHOI, D. L., SEO, J. H., CHUNG, K. S., HUH, G., KIM, J., CHOO, D. J., LEE, K. T. & LEE, J. Y. 2012. In vivo evaluation of oral anti-tumoral effect of 3,4-dihydroquinazoline derivative on solid tumor. *Bioorg Med Chem Lett*, 22, 1198-201.
- KAPOOR, N., BARTOSZEWSKI, R., QADRI, Y. J., BEBOK, Z., BUBIEN, J. K., FULLER, C. M. & BENOS, D. J. 2009. Knockdown of ASIC1 and epithelial sodium channel

- subunits inhibits glioblastoma whole cell current and cell migration. *J Biol Chem*, 284, 24526-41.
- KARAKURT, S. & ADALI, O. 2016. Tannic Acid Inhibits Proliferation, Migration, Invasion of Prostate Cancer and Modulates Drug Metabolizing and Antioxidant Enzymes. *Anticancer Agents Med Chem*, 16, 781-9.
- KEPP, O., MENGER, L., VACCHELLI, E., ADJEMIAN, S., MARTINS, I., MA, Y., SUKKURWALA, A. Q., MICHAUD, M., GALLUZZI, L., ZITVOGEL, L. & KROEMER, G. 2012. Anticancer activity of cardiac glycosides: At the frontier between cell-autonomous and immunological effects. *Oncoimmunology*, 1, 1640-1642.
- KHAJAH, M. A., MATHEW, P. M. & LUQMANI, Y. A. 2018. Na⁺/K⁺ ATPase activity promotes invasion of endocrine resistant breast cancer cells. *PLoS One*, 13, e0193779.
- KHATUN, A., FUJIMOTO, M., KITO, H., NIWA, S., SUZUKI, T. & OHYA, S. 2016. Down-Regulation of Ca²⁺-Activated K⁺ Channel K_{Ca} 1.1 in Human Breast Cancer MDA-MB-453 Cells Treated with Vitamin D Receptor Agonists. *International Journal of Molecular Sciences*, 17.
- KHATUN, A., SHIMOZAWA, M., KITO, H., KAWAGUCHI, M., FUJIMOTO, M., RI, M., KAJIKURI, J., NIWA, S., FUJII, M. & OHYA, S. 2018. Transcriptional Repression and Protein Degradation of the Ca(2+)-Activated K(+) Channel K(Ca)1.1 by Androgen Receptor Inhibition in Human Breast Cancer Cells. *Front Physiol*, 9, 312.
- KIM, C. J., CHO, Y. G., JEONG, S. W., KIM, Y. S., KIM, S. Y., NAM, S. W., LEE, S. H., YOO, N. J., LEE, J. Y. & PARK, W. S. 2004. Altered expression of KCNK9 in colorectal cancers. *Apmis*, 112, 588-94.
- KIM, I. Y., KANG, Y. J., YOON, M. J., KIM, E. H., KIM, S. U., KWON, T. K., KIM, I. A. & CHOI, K. S. 2011. Amiodarone sensitizes human glioma cells but not astrocytes to TRAIL-induced apoptosis via CHOP-mediated DR5 upregulation. *Neuro Oncol*, 13, 267-79.
- KISCHEL, P., GIRAULT, A., RODAT-DESPOIX, L., CHAMLALI, M., RADOSLAVOVA, S., ABOU DAYA, H., LEFEBVRE, T., FOULON, A., RYBARCZYK, P., HAGUE, F., DHENNIN-DUTHILLE, I., GAUTIER, M. & OUADID-AHIDOUCH, H. 2019. Ion Channels: New Actors Playing in Chemotherapeutic Resistance. *Cancers (Basel)*, 11.
- KLUMPP, D., FRANK, S. C., KLUMPP, L., SEZGIN, E. C., ECKERT, M., EDALAT, L., BASTMEYER, M., ZIPS, D., RUTH, P. & HUBER, S. M. 2017. TRPM8 is required for survival and radioresistance of glioblastoma cells. *Oncotarget*, 8, 95896-95913.
- KLUMPP, D., MISOVIC, M., SZTEYN, K., SHUMILINA, E., RUDNER, J. & HUBER, S. M. 2016. Targeting TRPM2 Channels Impairs Radiation-Induced Cell Cycle Arrest and Fosters Cell Death of T Cell Leukemia Cells in a Bcl-2-Dependent Manner. *Oxid Med Cell Longev*, 2016, 8026702.
- KONDRATSKA, K., KONDRATSKYI, A., YASSINE, M., LEMONNIER, L., LEPAGE, G., MORABITO, A., SKRYMA, R. & PREVARSKAYA, N. 2014. Orai1 and STIM1 mediate SOCE and contribute to apoptotic resistance of pancreatic adenocarcinoma. *Biochim Biophys Acta*, 1843, 2263-9.
- KOSTER, A. K., WOOD, C. A. P., THOMAS-TRAN, R., CHAVAN, T. S., ALMQVIST, J., CHOI, K. H., DU BOIS, J. & MADUKE, M. 2018. A selective class of inhibitors for the CLC-Ka chloride ion channel. *Proc Natl Acad Sci U S A*, 115, E4900-e4909.
- KOSZTKA, L., RUSZNÁK, Z., NAGY, D., NAGY, Z., FODOR, J., SZUCS, G., TELEK, A., GÖNCZI, M., RUZSNAVSZKY, O., SZENTANDRÁSSY, N. & CSERNOCH, L. 2011. Inhibition of TASK-3 (KCNK9) channel biosynthesis changes cell morphology and decreases both DNA content and mitochondrial function of melanoma cells maintained in cell culture. *Melanoma Res*, 21, 308-22.
- KOUBA, S., BRAIRE, J., FELIX, R., CHANTOME, A., JAFFRES, P. A., LEBRETON, J., DUBREUIL, D., PIPELIER, M., ZHANG, X., TREBAK, M., VANDIER, C., MATHE-ALLAINMAT, M. & POTIER-CARTEREAU, M. 2020. Lipidic synthetic alkaloids as SK3 channel modulators. Synthesis and biological evaluation of 2-substituted

- tetrahydropyridine derivatives with potential anti-metastatic activity. *Eur J Med Chem*, 186, 111854.
- KOVALENKO, I., GLASAUER, A., SCHÖCKEL, L., SAUTER, D. R. P., EHRMANN, A., SOHLER, F., HÄGEBARTH, A., NOVAK, I. & CHRISTIAN, S. 2016. Identification of KCa3.1 Channel as a Novel Regulator of Oxidative Phosphorylation in a Subset of Pancreatic Carcinoma Cell Lines. *PLoS one*, 11, e0160658-e0160658.
- KUNZELMANN, K., OUSINGSAWAT, J., BENEDETTO, R., CABRITA, I. & SCHREIBER, R. 2019. Contribution of Anoctamins to Cell Survival and Cell Death. *Cancers (Basel)*, 11.
- LAEZZA, C., D'ALESSANDRO, A., PALADINO, S., MARIA MALFITANO, A., CHIARA PROTO, M., GAZZERRO, P., PISANTI, S., SANTORO, A., CIAGLIA, E. & BIFULCO, M. 2012. Anandamide inhibits the Wnt/ β -catenin signalling pathway in human breast cancer MDA MB 231 cells. *Eur J Cancer*, 48, 3112-22.
- LANG, D. G., WANG, C. M. & COOPER, B. R. 1993. Lamotrigine, phenytoin and carbamazepine interactions on the sodium current present in N4TG1 mouse neuroblastoma cells. *J Pharmacol Exp Ther*, 266, 829-35.
- LANSU, K. & GENTILE, S. 2013. Potassium channel activation inhibits proliferation of breast cancer cells by activating a senescence program. *Cell death & disease*, 4, e652-e652.
- LASTRAIOLI, E., GUASTI, L., CROCIANI, O., POLVANI, S., HOFMANN, G., WITCHEL, H., BENCINI, L., CALISTRI, M., MESSERINI, L., SCATIZZI, M., MORETTI, R., WANKE, E., OLIVOTTO, M., MUGNAI, G. & ARCANGELI, A. 2004. hERG1 gene and HERG1 protein are overexpressed in colorectal cancers and regulate cell invasion of tumor cells. *Cancer Res*, 64, 606-11.
- LASTRAIOLI, E., TADDEI, A., MESSERINI, L., COMIN, C. E., FESTINI, M., GIANNELLI, M., TOMEZZOLI, A., PAGLIERANI, M., MUGNAI, G., DE MANZONI, G., BECHI, P. & ARCANGELI, A. 2006. hERG1 channels in human esophagus: evidence for their aberrant expression in the malignant progression of Barrett's esophagus. *J Cell Physiol*, 209, 398-404.
- LAURSEN, M., YATIME, L., NISSEN, P. & FEDOSOVA, N. U. 2013. Crystal structure of the high-affinity Na⁺K⁺-ATPase-ouabain complex with Mg²⁺ bound in the cation binding site. *Proc Natl Acad Sci U S A*, 110, 10958-63.
- LEANZA, L., BIASUTTO, L., MANAGO, A., GULBINS, E., ZORATTI, M. & SZABÒ, I. 2013a. Intracellular ion channels and cancer. *Frontiers in Physiology*, 4, 227.
- LEANZA, L., HENRY, B., SASSI, N., ZORATTI, M., CHANDY, K. G., GULBINS, E. & SZABÒ, I. 2012. Inhibitors of mitochondrial Kv1.3 channels induce Bax/Bak-independent death of cancer cells. *EMBO Molecular Medicine*, 4, 577-593.
- LEANZA, L., TRENTIN, L., BECKER, K. A., FREZZATO, F., ZORATTI, M., SEMENZATO, G., GULBINS, E. & SZABO, I. 2013b. Clofazimine, Psora-4 and PAP-1, inhibitors of the potassium channel Kv1.3, as a new and selective therapeutic strategy in chronic lymphocytic leukemia. *Leukemia*. England.
- LEE, A., FRASER, S. P. & DJAMGOZ, M. B. A. 2019a. Propranolol inhibits neonatal Nav1.5 activity and invasiveness of MDA-MB-231 breast cancer cells: Effects of combination with ranolazine. *Journal of Cellular Physiology*, 234, 23066-23081.
- LEE, H.-C., SU, M.-Y., LO, H.-C., WU, C.-C., HU, J.-R., LO, D.-M., CHAO, T.-Y., TSAI, H.-J. & DAI, M.-S. 2015. Cancer metastasis and EGFR signaling is suppressed by amiodarone-induced versican V2. *Oncotarget*, 6, 42976-42987.
- LEE, J. M., DAVIS, F. M., ROBERTS-THOMSON, S. J. & MONTEITH, G. R. 2011. Ion channels and transporters in cancer. 4. Remodeling of Ca²⁺ signaling in tumorigenesis: role of Ca²⁺ transport. *Am J Physiol Cell Physiol*, 301, C969-76.
- LEE, J. R., LEE, J. Y., KIM, H. J., HAHN, M. J., KANG, J. S. & CHO, H. 2019b. The inhibition of chloride intracellular channel 1 enhances Ca²⁺ and reactive oxygen species signaling in A549 human lung cancer cells. *Exp Mol Med*, 51, 81.

- LEHEN'KYI, V., FLOURAKIS, M., SKRYMA, R. & PREVARSKAYA, N. 2007. TRPV6 channel controls prostate cancer cell proliferation via Ca(2+)/NFAT-dependent pathways. *Oncogene*, 26, 7380-5.
- LEITHNER, K., HIRSCHMUGL, B., LI, Y., TANG, B., PAPP, R., NAGARAJ, C., STACHER, E., STIEGLER, P., LINDENMANN, J., OLSCHESKI, A., OLSCHESKI, H. & HRZENJAK, A. 2016. TASK-1 Regulates Apoptosis and Proliferation in a Subset of Non-Small Cell Lung Cancers. *PLoS One*, 11, e0157453.
- LEMIESZEK, M. K., STEPULAK, A., SAWA-WEJKSZA, K., CZERWONKA, A., IKONOMIDOU, C. & RZESKI, W. 2018. Riluzole Inhibits Proliferation, Migration and Cell Cycle Progression and Induces Apoptosis in Tumor Cells of Various Origins. *Anticancer Agents Med Chem*, 18, 565-572.
- LENKOWSKI, P. W., KO, S. H., ANDERSON, J. D., BROWN, M. L. & PATEL, M. K. 2004. Block of human NaV1.5 sodium channels by novel alpha-hydroxyphenylamide analogues of phenytoin. *Eur J Pharm Sci*, 21, 635-44.
- LESLIE, T. K., JAMES, A. D., ZACCAGNA, F., GRIST, J. T., DEEN, S., KENNERLEY, A., RIEMER, F., KAGGIE, J. D., GALLAGHER, F. A., GILBERT, F. J. & BRACKENBURY, W. J. 2019. Sodium homeostasis in the tumour microenvironment. *Biochim Biophys Acta Rev Cancer*, 1872, 188304.
- LI, L., FENG, R., XU, Q., ZHANG, F., LIU, T., CAO, J. & FEI, S. 2017. Expression of the beta3 subunit of Na(+)/K(+)-ATPase is increased in gastric cancer and regulates gastric cancer cell progression and prognosis via the PI3/AKT pathway. *Oncotarget*, 8, 84285-84299.
- LI, R., XIAO, C., LIU, H., HUANG, Y., DILGER, J. P. & LIN, J. 2018. Effects of local anesthetics on breast cancer cell viability and migration. *BMC cancer*, 18, 666-666.
- LI, T., CHEN, L., ZHAO, H., WU, L., MASTERS, J., HAN, C., HIROTA, K. & MA, D. 2019. Both Bupivacaine and Levobupivacaine inhibit colon cancer cell growth but not melanoma cells in vitro. *J Anesth*, 33, 17-25.
- LIGRESTI, A., MORIELLO, A. S., STAROWICZ, K., MATIAS, I., PISANTI, S., DE PETROCELLIS, L., LAEZZA, C., PORTELLA, G., BIFULCO, M. & DI MARZO, V. 2006. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther*, 318, 1375-87.
- LIN, S.-Y., CHANG, H.-H., LAI, Y.-H., LIN, C.-H., CHEN, M.-H., CHANG, G.-C., TSAI, M.-F. & CHEN, J. J. W. 2015. Digoxin Suppresses Tumor Malignancy through Inhibiting Multiple Src-Related Signaling Pathways in Non-Small Cell Lung Cancer. *PloS one*, 10, e0123305-e0123305.
- LIU, J., ZHANG, D., LI, Y., CHEN, W., RUAN, Z., DENG, L., WANG, L., TIAN, H., YIU, A., FAN, C., LUO, H., LIU, S., WANG, Y., XIAO, G., CHEN, L. & YE, W. 2013. Discovery of bufadienolides as a novel class of CIC-3 chloride channel activators with antitumor activities. *J Med Chem*, 56, 5734-43.
- LIU, X., ZOU, J., SU, J., LU, Y., ZHANG, J., LI, L. & YIN, F. 2016. Downregulation of transient receptor potential cation channel, subfamily C, member 1 contributes to drug resistance and high histological grade in ovarian cancer. *Int J Oncol*, 48, 243-52.
- LO, W. L., DONERMEYER, D. L. & ALLEN, P. M. 2012. A voltage-gated sodium channel is essential for the positive selection of CD4(+) T cells. *Nat Immunol*, 13, 880-7.
- LU, F., CHEN, H., ZHOU, C., LIU, S., GUO, M., CHEN, P., ZHUANG, H., XIE, D. & WU, S. 2008. T-type Ca2+ channel expression in human esophageal carcinomas: a functional role in proliferation. *Cell Calcium*, 43, 49-58.
- LUI, V. C., LUNG, S. S., PU, J. K., HUNG, K. N. & LEUNG, G. K. 2010. Invasion of human glioma cells is regulated by multiple chloride channels including CIC-3. *Anticancer Res*, 30, 4515-24.
- LUVETA, J., PARKS, R. M., HEERY, D. M., CHEUNG, K.-L. & JOHNSTON, S. J. 2020. Invasive Lobular Breast Cancer as a Distinct Disease: Implications for Therapeutic Strategy. *Oncology and Therapy*, 8, 1-11.
- MA, B., PAN, Y., SONG, Q., TIE, L., ZHANG, Y., XIAO, Y., ZHANG, J., HAN, J., XU, Y., XIANG, Y., YU, H.-M. & LI, X. 2011. The effect of topiramate on tumor-related

- angiogenesis and on the serum proteome of mice bearing Lewis lung carcinoma. *European journal of pharmacology*, 663, 9-16.
- MALAMAS, A. S., JIN, E., ZHANG, Q., HAAGA, J. & LU, Z.-R. 2015. Anti-angiogenic Effects of Bumetanide Revealed by DCE-MRI with a Biodegradable Macromolecular Contrast Agent in a Colon Cancer Model. *Pharmaceutical research*, 32, 3029-3043.
- MAMELAK, A. N., ROSENFELD, S., BUCHOLZ, R., RAUBITSCHKE, A., NABORS, L. B., FIVEASH, J. B., SHEN, S., KHAZAELI, M. B., COLCHER, D., LIU, A., OSMAN, M., GUTHRIE, B., SCHADE-BIJUR, S., HABLITZ, D. M., ALVAREZ, V. L. & GONDA, M. A. 2006. Phase I single-dose study of intracavitary-administered iodine-131-TM-601 in adults with recurrent high-grade glioma. *J Clin Oncol*, 24, 3644-50.
- MANTEGAZZA, M., CURIA, G., BIAGINI, G., RAGSDALE, D. S. & AVOLI, M. 2010. Voltage-gated sodium channels as therapeutic targets in epilepsy and other neurological disorders. *Lancet Neurol*, 9, 413-24.
- MAO, J., CHEN, L., XU, B., WANG, L., LI, H., GUO, J., LI, W., NIE, S. & JACOB, T. J. 2008. Suppression of CIC-3 channel expression reduces migration of nasopharyngeal carcinoma cells. *Biochem Pharmacol*, 75, 1706-16.
- MAO, J., YUAN, J., WANG, L., ZHANG, H., JIN, X., ZHU, J., LI, H., XU, B. & CHEN, L. 2013. Tamoxifen inhibits migration of estrogen receptor-negative hepatocellular carcinoma cells by blocking the swelling-activated chloride current. *J Cell Physiol*, 228, 991-1001.
- MARIOT, P., VANOVERBERGHE, K., LALEVEE, N., ROSSIER, M. F. & PREVARSKAYA, N. 2002. Overexpression of an alpha 1H (Cav3.2) T-type calcium channel during neuroendocrine differentiation of human prostate cancer cells. *J Biol Chem*, 277, 10824-33.
- MARTIN, F., UFODIAMA, C., WATT, I., BLAND, M. & BRACKENBURY, W. J. 2015. Therapeutic value of voltage-gated sodium channel inhibitors in breast, colorectal and prostate cancer: a systematic review. *Frontiers in Pharmacology*, 6, 273.
- MARTÍNEZ, R., STÜHMER, W., MARTIN, S., SCHELL, J., REICHMANN, A., ROHDE, V. & PARDO, L. 2015. Analysis of the expression of Kv10.1 potassium channel in patients with brain metastases and glioblastoma multiforme: impact on survival. *BMC Cancer*, 15, 839.
- MATTHEWS, H., RANSON, M. & KELSO, M. J. 2011. Anti-tumour/metastasis effects of the potassium-sparing diuretic amiloride: an orally active anti-cancer drug waiting for its call-of-duty? *Int J Cancer*, 129, 2051-61.
- MATULEF, K., HOWERY, A. E., TAN, L., KOBERTZ, W. R., DU BOIS, J. & MADUKE, M. 2008. Discovery of potent CLC chloride channel inhibitors. *ACS Chem Biol*, 3, 419-28.
- MAZZONE, A., EISENMAN, S. T., STREGE, P. R., YAO, Z., ORDOG, T., GIBBONS, S. J. & FARRUGIA, G. 2012. Inhibition of cell proliferation by a selective inhibitor of the Ca(2+)-activated Cl(-) channel, Ano1. *Biochem Biophys Res Commun*, 427, 248-53.
- MELÉNDEZ, T. A., HUANOSTA-GUTIÉRREZ, A., BARRIGA-MONTOYA, C., GONZÁLEZ-ANDRADE, M. & GÓMEZ-LAGUNAS, F. 2020. Dronedarone blockage of the tumor-related Kv10.1 channel: a comparison with amiodarone. *Pflügers Archiv - European Journal of Physiology*, 472, 75-87.
- MENG, Q., CHEN, X., SUN, L., ZHAO, C., SUI, G. & CAI, L. 2011. Carbamazepine promotes Her-2 protein degradation in breast cancer cells by modulating HDAC6 activity and acetylation of Hsp90. *Mol Cell Biochem*, 348, 165-71.
- MENGER, L., VACCHELLI, E., ADJEMIAN, S., MARTINS, I., MA, Y., SHEN, S., YAMAZAKI, T., SUKKURWALA, A. Q., MICHAUD, M., MIGNOT, G., SCHLEMMER, F., SULPICE, E., LOCHER, C., GIDROL, X., GHIRINGHELLI, F., MODJTAHEDI, N., GALLUZZI, L., ANDRÉ, F., ZITVOGEL, L., KEPP, O. & KROEMER, G. 2012. Cardiac glycosides exert anticancer effects by inducing immunogenic cell death. *Sci. Transl. Med.*, 4, 143ra99.

- METTS, J., BRADLEY, H. L., WANG, Z., SHAH, N. P., KAPUR, R., ARBISER, J. L. & BUNTING, K. D. 2017. Imipramine blue sensitively and selectively targets FLT3-ITD positive acute myeloid leukemia cells. *Scientific Reports*, 7, 4447.
- MOHR, C. J., GROSS, D., SEZGIN, E. C., STEUDEL, F. A., RUTH, P., HUBER, S. M. & LUKOWSKI, R. 2019. K(Ca)_{3.1} Channels Confer Radioresistance to Breast Cancer Cells. *Cancers*, 11, 1285.
- MOREELS, L., BHAT, C., VORACOVA, M., PEIGNEUR, S., GOOVAERTS, H., MAKI-LOHILUOMA, E., ZAHED, F., PARDO, L. A., YLI-KAUHALUOMA, J., KIURU, P. & TYTGAT, J. 2017a. Synthesis of novel purpurealidin analogs and evaluation of their effect on the cancer-relevant potassium channel KV10.1. *PLoS One*, 12, e0188811.
- MOREELS, L., PEIGNEUR, S., GALAN, D. T., DE PAUW, E., BERESS, L., WAELEKENS, E., PARDO, L. A., QUINTON, L. & TYTGAT, J. 2017b. APETx4, a Novel Sea Anemone Toxin and a Modulator of the Cancer-Relevant Potassium Channel KV10.1. *Mar Drugs*, 15.
- MU, D., CHEN, L., ZHANG, X., SEE, L. H., KOCH, C. M., YEN, C., TONG, J. J., SPIEGEL, L., NGUYEN, K. C., SERVOS, A., PENG, Y., PEI, L., MARKS, J. R., LOWE, S., HOEY, T., JAN, L. Y., MCCOMBIE, W. R., WIGLER, M. H. & POWERS, S. 2003. Genomic amplification and oncogenic properties of the KCNK9 potassium channel gene. *Cancer Cell*, 3, 297-302.
- MYCIELSKA, M. E., PALMER, C. P., BRACKENBURY, W. J. & DJAMGOZ, M. B. 2005. Expression of Na⁺-dependent citrate transport in a strongly metastatic human prostate cancer PC-3M cell line: regulation by voltage-gated Na⁺ channel activity. *J Physiol*, 563, 393-408.
- NABISSI, M., MORELLI, M. B., SANTONI, M. & SANTONI, G. 2012. Triggering of the TRPV2 channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents. *Carcinogenesis*, 34, 48-57.
- NAGY, D., GÖNCZI, M., DIENES, B., SZÖÖR, Á., FODOR, J., NAGY, Z., TÓTH, A., FODOR, T., BAI, P., SZÜCS, G., RUSZNÁK, Z. & CSERNOCH, L. 2014. Silencing the KCNK9 potassium channel (TASK-3) gene disturbs mitochondrial function, causes mitochondrial depolarization, and induces apoptosis of human melanoma cells. *Arch Dermatol Res*, 306, 885-902.
- NELSON, M., MILLICAN-SLATER, R., FORREST, L. C. & BRACKENBURY, W. J. 2014. The sodium channel beta1 subunit mediates outgrowth of neurite-like processes on breast cancer cells and promotes tumour growth and metastasis. *Int J Cancer*, 135, 2338-51.
- NELSON, M., YANG, M., DOWLE, A. A., THOMAS, J. R. & BRACKENBURY, W. J. 2015. The sodium channel-blocking antiepileptic drug phenytoin inhibits breast tumour growth and metastasis. *Mol Cancer*, 14, 13.
- NEMAN, J., TERMINI, J., WILCZYNSKI, S., VAIDEHI, N., CHOY, C., KOWOLIK, C. M., LI, H., HAMBRECHT, A. C., ROBERTS, E. & JANDIAL, R. 2014. Human breast cancer metastases to the brain display GABAergic properties in the neural niche. *Proc Natl Acad Sci U S A*, 111, 984-9.
- NGUYEN, C. H., HUTTARY, N., ATANASOV, A. G., CHATUPHONPRASERT, W., BRENNER, S., FRISTIOHADY, A., HONG, J., STADLER, S., HOLZNER, S., MILOVANOVIC, D., DIRSCH, V. M., KOPP, B., SAIKO, P., KRENN, L., JAGER, W. & KRUPITZA, G. 2017. Fenofibrate inhibits tumour intravasation by several independent mechanisms in a 3-dimensional co-culture model. *Int J Oncol*, 50, 1879-1888.
- NIE, F., LIANG, Y., JIANG, B., LI, X., XUN, H., HE, W., LAU, H. T. & MA, X. 2016. Apoptotic effect of tannic acid on fatty acid synthase over-expressed human breast cancer cells. *Tumour Biol*, 37, 2137-43.
- OLSEN, C. M., MEUSSEN-ELHOLM, E. T., ROSTE, L. S. & TAUBOLL, E. 2004. Antiepileptic drugs inhibit cell growth in the human breast cancer cell line MCF7. *Mol Cell Endocrinol*, 213, 173-9.

- OLSEN, M. L., SCHADE, S., LYONS, S. A., AMARAL, M. D. & SONTHEIMER, H. 2003. Expression of voltage-gated chloride channels in human glioma cells. *J Neurosci*, 23, 5572-82.
- ONGANER, P. U. & DJAMGOZ, M. B. 2005. Small-cell lung cancer (human): potentiation of endocytic membrane activity by voltage-gated Na⁺ channel expression in vitro. *J Membr Biol*, 204, 67-75.
- OOSTERWIJK, E. & GILLIES, R. J. 2014. Targeting ion transport in cancer. *Philos Trans R Soc Lond B Biol Sci*, 369, 20130107.
- OUADID-AHIDOUCH, H., AHIDOUCH, A. & PARDO, L. A. 2016. Kv10.1 K(+) channel: from physiology to cancer. *Pflugers Arch*, 468, 751-62.
- OUADID-AHIDOUCH, H., LE BOURHIS, X., ROUDBARAKI, M., TOILLON, R. A., DELCOURT, P. & PREVARSKAYA, N. 2001. Changes in the K⁺ current-density of MCF-7 cells during progression through the cell cycle: possible involvement of a h-ether.a-gogo K⁺ channel. *Receptors Channels*, 7, 345-56.
- OUSINGSAWAT, J., SPITZNER, M., PUNTHEERANURAK, S., TERRACCIANO, L., TORNILLO, L., BUBENDORF, L., KUNZELMANN, K. & SCHREIBER, R. 2007. Expression of voltage-gated potassium channels in human and mouse colonic carcinoma. *Clin Cancer Res*, 13, 824-31.
- OUWERKERK, R., JACOBS, M., MACURA, K., WOLFF, A., STEARNS, V., MEZBAN, S., KHOURI, N., BLUEMKE, D. & BOTTOMLEY, P. 2007. Elevated tissue sodium concentration in malignant breast lesions detected with non-invasive ²³Na MRI. *Breast Cancer Research and Treatment*, 106, 151-160.
- PANTZIARKA, P., SUKHATME, V., BOUCHE, G., MEHEUS, L. & SUKHATME, V. P. 2016. Repurposing Drugs in Oncology (ReDO)-diclofenac as an anti-cancer agent. *Ecancermedicalsecience*, 10, 610-610.
- PARDO, L. A., DEL CAMINO, D., SANCHEZ, A., ALVES, F., BRUGGEMANN, A., BECKH, S. & STUHMER, W. 1999. Oncogenic potential of EAG K(+) channels. *EMBO J*, 18, 5540-7.
- PARDO, L. A. & STUHMER, W. 2014. The roles of K(+) channels in cancer. *Nat Rev Cancer*, 14, 39-48.
- PARK, S.-H., CHUNG, Y. M., MA, J., YANG, Q., BEREK, J. S. & HU, M. C. T. 2016. Pharmacological activation of FOXO3 suppresses triple-negative breast cancer in vitro and in vivo. *Oncotarget*, 7, 42110-42125.
- PARKER, K. A., GLAYSHER, S., HURREN, J., KNIGHT, L. A., MCCORMICK, D., SUOVOURI, A., AMBERGER-MURPHY, V., PILKINGTON, G. J. & CREE, I. A. 2012. The effect of tricyclic antidepressants on cutaneous melanoma cell lines and primary cell cultures. *Anticancer Drugs*, 23, 65-9.
- PARKS, S. K., CHICHE, J. & POUYSSEGUR, J. 2013. Disrupting proton dynamics and energy metabolism for cancer therapy. *Nat Rev Cancer*, 13, 611-23.
- PELLEGRINO, M., RIZZA, P., NIGRO, A., CERARDI, R., RICCI, E., PERROTTA, I., AQUILA, S., LANZINO, M., ANDO, S., MORELLI, C. & SISI, D. 2018. FoxO3a Mediates the Inhibitory Effects of the Antiepileptic Drug Lamotrigine on Breast Cancer Growth. *Mol Cancer Res*, 16, 923-934.
- PERUZZO, R., BIASUTTO, L., SZABÒ, I. & LEANZA, L. 2016. Impact of intracellular ion channels on cancer development and progression. *European biophysics journal : EBJ*, 45, 685-707.
- PERUZZO, R. & SZABO, I. 2019. Contribution of Mitochondrial Ion Channels to Chemo-Resistance in Cancer Cells. *Cancers*, 11, 761.
- PETERS, A. A., MILEVSKIY, M. J., LEE, W. C., CURRY, M. C., SMART, C. E., SAUNUS, J. M., REID, L., DA SILVA, L., MARCIAL, D. L., DRAY, E., BROWN, M. A., LAKHANI, S. R., ROBERTS-THOMSON, S. J. & MONTEITH, G. R. 2016. The calcium pump plasma membrane Ca(2+)-ATPase 2 (PMCA2) regulates breast cancer cell proliferation and sensitivity to doxorubicin. *Sci Rep*, 6, 25505.
- PILLOZZI, S., BRIZZI, M. F., BALZI, M., CROCIANI, O., CHERUBINI, A., GUASTI, L., BARTOLOZZI, B., BECCHETTI, A., WANKE, E., BERNABEI, P. A., OLIVOTTO, M.,

- PEGORARO, L. & ARCANGELI, A. 2002. HERG potassium channels are constitutively expressed in primary human acute myeloid leukemias and regulate cell proliferation of normal and leukemic hemopoietic progenitors. *Leukemia*, 16, 1791-8.
- PILLOZZI, S., BRIZZI, M. F., BERNABEI, P. A., BARTOLOZZI, B., CAPORALE, R., BASILE, V., BODDI, V., PEGORARO, L., BECCHETTI, A. & ARCANGELI, A. 2007. VEGFR-1 (FLT-1), beta1 integrin, and hERG K⁺ channel for a macromolecular signaling complex in acute myeloid leukemia: role in cell migration and clinical outcome. *Blood*, 110, 1238-50.
- PILLOZZI, S., D'AMICO, M., BARTOLI, G., GASPAROLI, L., PETRONI, G., CROCIANI, O., MARZO, T., GUERRIERO, A., MESSORI, L., SEVERI, M., UDISTI, R., WULFF, H., CHANDY, K. G., BECCHETTI, A. & ARCANGELI, A. 2018. The combined activation of K(Ca)_{3.1} and inhibition of K(v)_{11.1}/hERG1 currents contribute to overcome Cisplatin resistance in colorectal cancer cells. *Br J Cancer*, 118, 200-212.
- PILLOZZI, S., MASSELLI, M., DE LORENZO, E., ACCORDI, B., CILIA, E., CROCIANI, O., AMEDEI, A., VELTRONI, M., D'AMICO, M., BASSO, G., BECCHETTI, A., CAMPANA, D. & ARCANGELI, A. 2011. Chemotherapy resistance in acute lymphoblastic leukemia requires hERG1 channels and is overcome by hERG1 blockers. *Blood*, 117, 902-14.
- PILLOZZI, S., MASSELLI, M., GASPAROLI, L., D'AMICO, M., POLLETTA, L., VELTRONI, M., FAVRE, C., BASSO, G., BECCHETTI, A. & ARCANGELI, A. 2016. Macrolide antibiotics exert antileukemic effects by modulating the autophagic flux through inhibition of hERG1 potassium channels. *Blood Cancer J*, 6, e423.
- PONGRAKHANANON, V., CHUNHACHA, P. & CHANVORACHOTE, P. 2013. Ouabain suppresses the migratory behavior of lung cancer cells. *PLoS One*, 8, e68623.
- POPOV, S., VENETSANO, K., CHEDRESE, P., PINTO, V., TAKEMORI, H., FRANCO-CERECEDA, A., ERIKSSON, P., MOCHIZUKI, N., SOARES-DA-SILVA, P. & BERTORELLO, A. 2012. Increases in intracellular sodium activate transcription and gene expression via the salt-inducible kinase 1 network in an atrial myocyte cell line. *American Journal Of Physiology. Heart And Circulatory Physiology*, 303, H57-H65.
- POST, R. L., KUME, S., TOBIN, T., ORCUTT, B. & SEN, A. K. 1969. Flexibility of an active center in sodium-plus-potassium adenosine triphosphatase. *The Journal of general physiology*, 54, 306-326.
- POTIER, M., JOULIN, V., ROGER, S., BESSON, P., JOURDAN, M. L., LEGUENNEC, J. Y., BOUGNOUX, P. & VANDIER, C. 2006. Identification of SK3 channel as a new mediator of breast cancer cell migration. *Mol Cancer Ther*, 5, 2946-53.
- POUPON, L., LAMOINE, S., PEREIRA, V., BARRIERE, D. A., LOLIGNIER, S., GIRAUDET, F., AISSOUNI, Y., MELEINE, M., PRIVAL, L., RICHARD, D., KERCKHOVE, N., AUTHIER, N., BALAYSSAC, D., ESCHALIER, A., LAZDUNSKI, M. & BUSSEROLLES, J. 2018. Targeting the TREK-1 potassium channel via riluzole to eliminate the neuropathic and depressive-like effects of oxaliplatin. *Neuropharmacology*, 140, 43-61.
- PREVARSKAYA, N., SKRYMA, R. & SHUBA, Y. 2011. Calcium in tumour metastasis: new roles for known actors. *Nat Rev Cancer*, 11, 609-18.
- QUAST, S. A., BERGER, A., BUTTSTÄDT, N., FRIEBEL, K., SCHÖNHERR, R. & EBERLE, J. 2012. General Sensitization of melanoma cells for TRAIL-induced apoptosis by the potassium channel inhibitor TRAM-34 depends on release of SMAC. *PLoS One*, 7, e39290.
- RADERER, M., DEPISCH, D., HAIDER, K., KWASNY, W., DJAVANMARD, M. & SCHEITHAUER, W. 1993. A Phase I/II Study of Quinidine, a Potential Multidrug Resistance-Reversing Agent, in Combination with Pirarubicin in Patients with Advanced Refractory Breast Cancer. *Oncology Research and Treatment*, 16, 450-453.
- RAJAMANICKAM, S., PANNEERDOSS, S., GORTHI, A., TIMILSINA, S., ONYEAGUCHA, B., KOVALSKYY, D., IVANOV, D., HANES, M. A., VADLAMUDI, R. K., CHEN, Y., BISHOP, A. J., ARBISER, J. L. & RAO, M. K. 2016. Inhibition of FoxM1-Mediated

- DNA Repair by Imipramine Blue Suppresses Breast Cancer Growth and Metastasis. *Clin Cancer Res*, 22, 3524-36.
- REDDY, J. P., DAWOOD, S., MITCHELL, M., DEBEB, B. G., BLOOM, E., GONZALEZ-ANGULO, A. M., SULMAN, E. P., BUCHHOLZ, T. A. & WOODWARD, W. A. 2015. Antiepileptic drug use improves overall survival in breast cancer patients with brain metastases in the setting of whole brain radiotherapy. *Radiother Oncol*, 117, 308-14.
- RIM, H. K., CHO, S., SHIN, D. H., CHUNG, K. S., CHO, Y. W., CHOI, J. H., LEE, J. Y. & LEE, K. T. 2014. T-type Ca²⁺ channel blocker, KYS05090 induces autophagy and apoptosis in A549 cells through inhibiting glucose uptake. *Molecules*, 19, 9864-75.
- ROGER, S., BESSON, P. & LE GUENNEC, J. Y. 2003. Involvement of a novel fast inward sodium current in the invasion capacity of a breast cancer cell line. *Biochim Biophys Acta*, 1616, 107-11.
- ROGER, S., JELASSI, B., COUILLIN, I., PELEGRIN, P., BESSON, P. & JIANG, L. H. 2015. Understanding the roles of the P2X7 receptor in solid tumour progression and therapeutic perspectives. *Biochim Biophys Acta*, 1848, 2584-602.
- ROGER, S., LE GUENNEC, J.-Y. & BESSON, P. 2004. Particular sensitivity to calcium channel blockers of the fast inward voltage-dependent sodium current involved in the invasive properties of a metastatic breast cancer cell line. *British journal of pharmacology*, 141, 610-615.
- ROJAS, E., CORCHETE, L., SAN SEGUNDO, L., MARTÍNEZ-BLANCH, J. F., CODOÑER, F. M., PAÍNO, T., PUIG, N., GARCÍA-SANZ, R., MATEOS, M. V., OCIO, E. M., MISIEWICZ-KRZEMINSKA, I. & GUTIÉRREZ, N. C. 2017. Amiloride, an old diuretic drug, is a potential therapeutic agent for multiple myeloma. *Clinical Cancer Research*, clincanres.0678.2017.
- RU, Q., TIAN, X., PI, M. S., CHEN, L., YUE, K., XIONG, Q., MA, B. M. & LI, C. Y. 2015. Voltagegated K⁺ channel blocker quinidine inhibits proliferation and induces apoptosis by regulating expression of microRNAs in human glioma U87MG cells. *Int J Oncol*, 46, 833-40.
- SALES, T. T., RESENDE, F. F., CHAVES, N. L., TITZE-DE-ALMEIDA, S. S., BAO, S. N., BRETTAS, M. L. & TITZE-DE-ALMEIDA, R. 2016. Suppression of the Eag1 potassium channel sensitizes glioblastoma cells to injury caused by temozolomide. *Oncol Lett*, 12, 2581-2589.
- SATO, K., ISHIZUKA, J., COOPER, C. W., CHUNG, D. H., TSUCHIYA, T., UCHIDA, T., RAJARAMAN, S., TOWNSEND, C. M., JR. & THOMPSON, J. C. 1994. Inhibitory effect of calcium channel blockers on growth of pancreatic cancer cells. *Pancreas*, 9, 193-202.
- SAUTER, D. R. P., NOVAK, I., PEDERSEN, S. F., LARSEN, E. H. & HOFFMANN, E. K. 2015. ANO1 (TMEM16A) in pancreatic ductal adenocarcinoma (PDAC). *Pflugers Archiv : European journal of physiology*, 467, 1495-1508.
- SCHMEEL, L. C., SCHMEEL, F. C., KIM, Y., BLAUM-FEDER, S., ENDO, T. & SCHMIDT-WOLF, I. G. 2015. Flunarizine exhibits in vitro efficacy against lymphoma and multiple myeloma cells. *Anticancer Res*, 35, 1369-76.
- SCHNEDITZ, G., ELIAS, J. E., PAGANO, E., ZAEEM CADER, M., SAVELJEVA, S., LONG, K., MUKHOPADHYAY, S., ARASTEH, M., LAWLEY, T. D., DOUGAN, G., BASSETT, A., KARLSEN, T. H., KASER, A. & KANEIDER, N. C. 2019. GPR35 promotes glycolysis, proliferation, and oncogenic signaling by engaging with the sodium potassium pump. *Sci. Signal.*, 12.
- SCHWAB, A., FABIAN, A., HANLEY, P. J. & STOCK, C. 2012. Role of ion channels and transporters in cell migration. *Physiol Rev*, 92, 1865-913.
- SEO, Y., KIM, J., CHANG, J., KIM, S. S., NAMKUNG, W. & KIM, I. 2018. Synthesis and biological evaluation of novel Ani9 derivatives as potent and selective ANO1 inhibitors. *European Journal of Medicinal Chemistry*, 160, 245-255.
- SEO, Y., PARK, J., KIM, M., LEE, H. K., KIM, J. H., JEONG, J. H. & NAMKUNG, W. 2015. Inhibition of ANO1/TMEM16A Chloride Channel by Idebenone and Its Cytotoxicity to Cancer Cell Lines. *PLoS One*, 10, e0133656.

- SEO, Y., RYU, K., PARK, J., JEON, D.-K., JO, S., LEE, H. K. & NAMKUNG, W. 2017. Inhibition of ANO1 by luteolin and its cytotoxicity in human prostate cancer PC-3 cells. *PLoS one*, 12, e0174935-e0174935.
- SEOL, H. S., LEE, S. E., SONG, J. S., LEE, H. Y., PARK, S., KIM, I., SINGH, S. R., CHANG, S. & JANG, S. J. 2016. Glutamate release inhibitor, Riluzole, inhibited proliferation of human hepatocellular carcinoma cells by elevated ROS production. *Cancer Lett*, 382, 157-165.
- SETTE, A., SPADAVECCHIA, J., LANDOULSI, J., CASALE, S., HAYE, B., CROCIANI, O. & ARCANGELI, A. 2013. Development of novel anti-Kv 11.1 antibody-conjugated PEG-TiO₂ nanoparticles for targeting pancreatic ductal adenocarcinoma cells. *J Nanopart Res*, 15, 2111.
- SEZZI, M. L., DE LUCA, G., MATERAZZI, M. & BELLELLI, L. 1985. Effects of a calcium-antagonist (flunarizine) on cancer cell movement and phagocytosis. *Anticancer Res*, 5, 265-71.
- SHAO, X.-D., WU, K., HAO, Z.-M., HONG, L., ZHANG, J. & FAN, D. 2005. The potent inhibitory effects of cisapride, a specific blocker for human ether-a-go-go-related gene (HERG) channel, on gastric cancer cells. *Cancer Biology & Therapy*, 4, 295-301.
- SHAPOVALOV, G., RITAINE, A., SKRYMA, R. & PREVARSKAYA, N. 2016. Role of TRP ion channels in cancer and tumorigenesis. *Semin Immunopathol*, 38, 357-69.
- SHEN, J.-J., ZHAN, Y.-C., LI, H.-Y. & WANG, Z. 2020. Ouabain impairs cancer metabolism and activates AMPK-Src signaling pathway in human cancer cell lines. *Acta Pharmacologica Sinica*, 41, 110-118.
- SHEN, M. R., DROOGMANS, G., EGGERMONT, J., VOETS, T., ELLORY, J. C. & NILIUS, B. 2000. Differential expression of volume-regulated anion channels during cell cycle progression of human cervical cancer cells. *J Physiol*, 529 Pt 2, 385-94.
- SHI, X. N., LI, H., YAO, H., LIU, X., LI, L., LEUNG, K. S., KUNG, H. F., LU, D., WONG, M. H. & LIN, M. C. 2015. In Silico Identification and In Vitro and In Vivo Validation of Anti-Psychotic Drug Fluspirilene as a Potential CDK2 Inhibitor and a Candidate Anti-Cancer Drug. *PLoS One*, 10, e0132072.
- SHIN, D. H., LEEM, D. G., SHIN, J. S., KIM, J. I., KIM, K. T., CHOI, S. Y., LEE, M. H., CHOI, J. H. & LEE, K. T. 2018. Compound K induced apoptosis via endoplasmic reticulum Ca(2+) release through ryanodine receptor in human lung cancer cells. *J Ginseng Res*, 42, 165-174.
- SIEKMANN, W., TINA, E., VON SYDOW, A. K. & GUPTA, A. 2019. Effect of lidocaine and ropivacaine on primary (SW480) and metastatic (SW620) colon cancer cell lines. *Oncol Lett*, 18, 395-401.
- SIMON, A., YANG, M., MARRISON, J. L., JAMES, A. D., HUNT, M. J., O'TOOLE, P. J., KAYE, P. M., WHITTINGTON, M. A., CHAWLA, S. & BRACKENBURY, W. J. 2020. Metastatic breast cancer cells induce altered microglial morphology and electrical excitability in vivo. *J Neuroinflammation*, 17, 87.
- SINGH, H., STEFANI, E. & TORO, L. 2012. Intracellular BK(Ca) (iBK(Ca)) channels. *J Physiol*, 590, 5937-47.
- SONG, Y., GAO, J., GUAN, L., CHEN, X., GAO, J. & WANG, K. 2018. Inhibition of ANO1/TMEM16A induces apoptosis in human prostate carcinoma cells by activating TNF- α signaling. *Cell Death & Disease*, 9, 703.
- SPARKS, R. L., POOL, T. B., SMITH, N. K. & CAMERON, I. L. 1983. Effects of amiloride on tumor growth and intracellular element content of tumor cells in vivo. *Cancer Res*, 43, 73-7.
- SPEYER, C. L., SMITH, J. S., BANDA, M., DEVRIES, J. A., MEKANI, T. & GORSKI, D. H. 2012. Metabotropic glutamate receptor-1: a potential therapeutic target for the treatment of breast cancer. *Breast Cancer Res Treat*, 132, 565-73.
- SQUECCO, R., TANI, A., ZECCHI-ORLANDINI, S., FORMIGLI, L. & FRANCINI, F. 2015. Melatonin affects voltage-dependent calcium and potassium currents in MCF-7 cell line cultured either in growth or differentiation medium. *Eur J Pharmacol*, 758, 40-52.

- STETTNER, M., KRAMER, G., STRAUSS, A., KVITKINA, T., OHLE, S., KIESEIER, B. C. & THELEN, P. 2012. Long-term antiepileptic treatment with histone deacetylase inhibitors may reduce the risk of prostate cancer. *Eur J Cancer Prev*, 21, 55-64.
- SU, C.-K., CHOU, C.-T., LIN, K.-L., LIANG, W.-Z., CHENG, J.-S., CHANG, H.-T., CHEN, I. S., LU, T., KUO, C.-C., YU, C.-C., SHIEH, P., KUO, D.-H., CHEN, F.-A. & JAN, C.-R. 2016. Effect of protriptyline on $[Ca^{2+}]_i$ and viability in MG63 human osteosarcoma cells. *Toxicology Mechanisms and Methods*, 26, 580-587.
- SUN, H., LUO, L., LAL, B., MA, X., CHEN, L., HANN, C. L., FULTON, A. M., LEAHY, D. J., LATERRA, J. & LI, M. 2016. A monoclonal antibody against KCNK9 K(+) channel extracellular domain inhibits tumour growth and metastasis. *Nat Commun*, 7, 10339.
- SUN, R., HE, X., JIANG, X. & TAO, H. 2019. The new role of riluzole in the treatment of pancreatic cancer through the apoptosis and autophagy pathways. *J Cell Biochem*.
- SUN, X., WEI, Q., CHENG, J., BIAN, Y., TIAN, C., HU, Y. & LI, H. 2017. Enhanced Stim1 expression is associated with acquired chemo-resistance of cisplatin in osteosarcoma cells. *Hum Cell*, 30, 216-225.
- SUN, Y. H., GAO, X., TANG, Y. J., XU, C. L. & WANG, L. H. 2006. Androgens induce increases in intracellular calcium via a G protein-coupled receptor in LNCaP prostate cancer cells. *J Androl*, 27, 671-8.
- SZABÓ, I., BOCK, J., GRASSMÉ, H., SODDEMANN, M., WILKER, B., LANG, F., ZORATTI, M. & GULBINS, E. 2008. Mitochondrial potassium channel Kv1.3 mediates Bax-induced apoptosis in lymphocytes. *Proc Natl Acad Sci U S A*, 105, 14861-6.
- SZABÓ, I., SODDEMANN, M., LEANZA, L., ZORATTI, M. & GULBINS, E. 2011. Single-point mutations of a lysine residue change function of Bax and Bcl-xL expressed in Bax- and Bak-less mouse embryonic fibroblasts: novel insights into the molecular mechanisms of Bax-induced apoptosis. *Cell Death Differ*, 18, 427-38.
- TAKADA, M., FUJIMOTO, M., MOTOMURA, H. & HOSOMI, K. 2016. Inverse Association between Sodium Channel-Blocking Antiepileptic Drug Use and Cancer: Data Mining of Spontaneous Reporting and Claims Databases. *Int J Med Sci*, 13, 48-59.
- TEICHMANN, M., KRETSCHY, N., KOPF, S., JARUKAMJORN, K., ATANASOV, A. G., VIOLA, K., GIESSRIGL, B., SAIKO, P., SZEKERES, T., MIKULITS, W., DIRSCH, V. M., HUTTARY, N., KRIEGER, S., JAGER, W., GRUSCH, M., DOLZNIG, H. & KRUPITZA, G. 2014. Inhibition of tumour spheroid-induced prometastatic intravasation gates in the lymph endothelial cell barrier by carbamazepine: drug testing in a 3D model. *Arch Toxicol*, 88, 691-9.
- THEBAULT, S., FLOURAKIS, M., VANOVERBERGHE, K., VANDERMOERE, F., ROUDBARAKI, M., LEHEN'KYI, V., SLOMIANNY, C., BECK, B., MARIOT, P., BONNAL, J. L., MAUROY, B., SHUBA, Y., CAPIOD, T., SKRYMA, R. & PREVARSKAYA, N. 2006. Differential role of transient receptor potential channels in Ca^{2+} entry and proliferation of prostate cancer epithelial cells. *Cancer Res*, 66, 2038-47.
- THOMAS, D., GUT, B., KARSAI, S., WIMMER, A. B., WU, K., WENDT-NORDAHL, G., ZHANG, W., KATHOFER, S., SCHOELS, W., KATUS, H. A., KIEHN, J. & KARLE, C. A. 2003. Inhibition of cloned HERG potassium channels by the antiestrogen tamoxifen. *Naunyn Schmiedebergs Arch Pharmacol*, 368, 41-8.
- THURBER, A. E., NELSON, M., FROST, C. L., LEVIN, M., BRACKENBURY, W. J. & KAPLAN, D. L. 2017. IK channel activation increases tumor growth and induces differential behavioral responses in two breast epithelial cell lines. *Oncotarget*, 8, 42382-42397.
- TIMAR, J., CHOPRA, H., RONG, X., HATFIELD, J. S., FLIGIEL, S. E., ONODA, J. M., TAYLOR, J. D. & HONN, K. V. 1992. Calcium channel blocker treatment of tumor cells induces alterations in the cytoskeleton, mobility of the integrin α IIb β 3 and tumor-cell-induced platelet aggregation. *J Cancer Res Clin Oncol*, 118, 425-34.
- TURNER, K. L., HONASOGE, A., ROBERT, S. M., MCFERRIN, M. M. & SONTHEIMER, H. 2014. A proinvasive role for the Ca^{2+} -activated K(+) channel KCa3.1 in malignant glioma. *Glia*, 62, 971-81.

- URREGO, D., TOMCZAK, A. P., ZAHED, F., STUHMER, W. & PARDO, L. A. 2014. Potassium channels in cell cycle and cell proliferation. *Philos Trans R Soc Lond B Biol Sci*, 369, 20130094.
- UZUN, S., ALTUN, S. & BUGAN, İ. 2017. Anti-metastatic effect of riluzole on Mat-LyLu rat prostate cancer cell line. *Annals of Oncology*, 28, x3.
- VALERIE, N. C., DZIEGIELEWSKA, B., HOSING, A. S., AUGUSTIN, E., GRAY, L. S., BRAUTIGAN, D. L., LARNER, J. M. & DZIEGIELEWSKI, J. 2013. Inhibition of T-type calcium channels disrupts Akt signaling and promotes apoptosis in glioblastoma cells. *Biochem Pharmacol*, 85, 888-97.
- VAN DER HOEVEN, D., CHO, K.-J., MA, X., CHIGURUPATI, S., PARTON, R. G. & HANCOCK, J. F. 2013. Fendiline Inhibits K-Ras Plasma Membrane Localization and Blocks K-Ras Signal Transmission. *Molecular and Cellular Biology*, 33, 237.
- VANDENBERG, J. I., PERRY, M. D., PERRIN, M. J., MANN, S. A., KE, Y. & HILL, A. P. 2012. hERG K(+) channels: structure, function, and clinical significance. *Physiol Rev*, 92, 1393-478.
- VILA-CARRILES, W. H., KOVACS, G. G., JOVOV, B., ZHOU, Z.-H., PAHWA, A. K., COLBY, G., ESIMAI, O., GILLESPIE, G. Y., MAPSTONE, T. B., MARKERT, J. M., FULLER, C. M., BUBIEN, J. K. & BENOS, D. J. 2006. Surface expression of ASIC2 inhibits the amiloride-sensitive current and migration of glioma cells. *J. Biol. Chem.*, 281, 19220-19232.
- VODNALA, S. K., EIL, R., KISHTON, R. J., SUKUMAR, M., YAMAMOTO, T. N., HA, N. H., LEE, P. H., SHIN, M., PATEL, S. J., YU, Z., PALMER, D. C., KRUHLAK, M. J., LIU, X., LOCASALE, J. W., HUANG, J., ROYCHOUDHURI, R., FINKEL, T., KLEBANOFF, C. A. & RESTIFO, N. P. 2019. T cell stemness and dysfunction in tumors are triggered by a common mechanism. *Science*, 363, eaau0135.
- VOLOSHYNA, I., BESANA, A., CASTILLO, M., MATOS, T., WEINSTEIN, I. B., MANSUKHANI, M., ROBINSON, R. B., CORDON-CARDO, C. & FEINMARK, S. J. 2008. TREK-1 is a novel molecular target in prostate cancer. *Cancer Res*, 68, 1197-203.
- WALKER, A. J., CARD, T., BATES, T. E. & MUIR, K. 2011. Tricyclic antidepressants and the incidence of certain cancers: a study using the GPRD. *Br J Cancer*, 104, 193-7.
- WANG, G. X., HATTON, W. J., WANG, G. L., ZHONG, J., YAMBOLIEV, I., DUAN, D. & HUME, J. R. 2003. Functional effects of novel anti-CIC-3 antibodies on native volume-sensitive osmolyte and anion channels in cardiac and smooth muscle cells. *Am J Physiol Heart Circ Physiol*, 285, H1453-63.
- WANG, H., ZHANG, Y., CAO, L., HAN, H., WANG, J., YANG, B., NATTEL, S. & WANG, Z. 2002. HERG K⁺ channel, a regulator of tumor cell apoptosis and proliferation. *Cancer Res*, 62, 4843-8.
- WANG, J., XU, Y. Q., LIANG, Y. Y., GONGORA, R., WARNOCK, D. G. & MA, H. P. 2007. An intermediate-conductance Ca(2⁺)-activated K⁺ channel mediates B lymphoma cell cycle progression induced by serum. *Pflugers Arch*, 454, 945-56.
- WANG, L., MA, W., ZHU, L., YE, D., LI, Y., LIU, S., LI, H., ZUO, W., LI, B., YE, W. & CHEN, L. 2012. CIC-3 is a candidate of the channel proteins mediating acid-activated chloride currents in nasopharyngeal carcinoma cells. *Am J Physiol Cell Physiol*, 303, C14-23.
- WANG, Y., LONARD, D. M., YU, Y., CHOW, D. C., PALZKILL, T. G., WANG, J., QI, R., MATZUK, A. J., SONG, X., MADOUX, F., HODDER, P., CHASE, P., GRIFFIN, P. R., ZHOU, S., LIAO, L., XU, J. & O'MALLEY, B. W. 2014. Bufalin is a potent small-molecule inhibitor of the steroid receptor coactivators SRC-3 and SRC-1. *Cancer Res*, 74, 1506-1517.
- WANG, Y., YANG, Z., MENG, Z., CAO, H., ZHU, G., LIU, T. & WANG, X. 2013. Knockdown of TRPM8 suppresses cancer malignancy and enhances epirubicin-induced apoptosis in human osteosarcoma cells. *Int J Biol Sci*, 10, 90-102.
- WANNOUS, R., BON, E., GILLET, L., CHAMOUTON, J., WEBER, G., BRISSON, L., GORE, J., BOUGNOUX, P., BESSON, P., ROGER, S. & CHEVALIER, S. 2015. Suppression

- of PPARbeta, and DHA treatment, inhibit Nav1.5 and NHE-1 pro-invasive activities. *Pflugers Arch*, 467, 1249-59.
- WATKINS, S. & SONTHEIMER, H. 2011. Hydrodynamic cellular volume changes enable glioma cell invasion. *J Neurosci*, 31, 17250-9.
- WEAVER, A. K., LIU, X. & SONTHEIMER, H. 2004. Role for calcium-activated potassium channels (BK) in growth control of human malignant glioma cells. *J Neurosci Res*, 78, 224-34.
- WHELER, J. J., JANKU, F., FALCHOOK, G. S., JACKSON, T. L., FU, S., NAING, A., TSIMBERIDOU, A. M., MOULDER, S. L., HONG, D. S., YANG, H., PIHA-PAUL, S. A., ATKINS, J. T., GARCIA-MANERO, G. & KURZROCK, R. 2014. Phase I study of anti-VEGF monoclonal antibody bevacizumab and histone deacetylase inhibitor valproic acid in patients with advanced cancers. *Cancer Chemother Pharmacol*, 73, 495-501.
- WILLIAMS, S., BATEMAN, A. & O'KELLY, I. 2013. Altered expression of two-pore domain potassium (K2P) channels in cancer. *PLoS One*, 8, e74589.
- WILSON, L. E., D'ALOISIO, A. A., SANDLER, D. P. & TAYLOR, J. A. 2016. Long-term use of calcium channel blocking drugs and breast cancer risk in a prospective cohort of US and Puerto Rican women. *Breast Cancer Res*, 18, 61.
- WONDERLIN, W. F., WOODFORK, K. A. & STROBL, J. S. 1995. Changes in membrane potential during the progression of MCF-7 human mammary tumor cells through the cell cycle. *J Cell Physiol*, 165, 177-85.
- WOODS, N., TREVINO, J., COPPOLA, D., CHELLAPPAN, S., YANG, S. & PADMANABHAN, J. 2015. Fendiline inhibits proliferation and invasion of pancreatic cancer cells by interfering with ADAM10 activation and β -catenin signaling. *Oncotarget*, 6, 35931-35948.
- WU, Y., GAO, B., XIONG, Q.-J., WANG, Y.-C., HUANG, D.-K. & WU, W.-N. 2017. Acid-sensing ion channels contribute to the effect of extracellular acidosis on proliferation and migration of A549 cells. *Tumor Biology*, 39.
- XIA, Z., BERGSTRAND, A., DEPIERRE, J. W. & NASSBERGER, L. 1999. The antidepressants imipramine, clomipramine, and citalopram induce apoptosis in human acute myeloid leukemia HL-60 cells via caspase-3 activation. *J Biochem Mol Toxicol*, 13, 338-47.
- XIE, B., ZHAO, R., BAI, B., WU, Y., XU, Y., LU, S., FANG, Y., WANG, Z., MASWIKITI, E. P., ZHOU, X., PAN, H. & HAN, W. 2018. Identification of key tumorigenesis related genes and their microRNAs in colon cancer. *Oncol Rep*, 40, 3551-3560.
- XIE, C., LIU, G., LIU, J., HUANG, Z., WANG, F., LEI, X., WU, X., HUANG, S., ZHONG, D. & XU, X. 2012. Anti-proliferative effects of anandamide in human hepatocellular carcinoma cells. *Oncology letters*, 4, 403-407.
- XU, G., FANG, Z., CLARK, L. H., SUN, W., YIN, Y., ZHANG, R., SULLIVAN, S. A., TRAN, A. Q., KONG, W., WANG, J., ZHOU, C. & BAE-JUMP, V. L. 2018. Topiramate exhibits anti-tumorigenic and metastatic effects in ovarian cancer cells. *Am J Transl Res*, 10, 1663-1676.
- XU, S., LIU, C., MA, Y., JI, H. L. & LI, X. 2016. Potential Roles of Amiloride-Sensitive Sodium Channels in Cancer Development. *Biomed Res Int*, 2016, 2190216.
- XUAN, W., ZHAO, H., HANKIN, J., CHEN, L., YAO, S. & MA, D. 2016. Local anesthetic bupivacaine induced ovarian and prostate cancer apoptotic cell death and underlying mechanisms in vitro. *Scientific reports*, 6, 26277-26277.
- XUE, H., WANG, Y., MACCORMACK, T. J., LUTES, T., RICE, C., DAVEY, M., DUGOURD, D., ILENCHUK, T. T. & STEWART, J. M. 2018. Inhibition of Transient Receptor Potential Vanilloid 6 channel, elevated in human ovarian cancers, reduces tumour growth in a xenograft model. *J Cancer*, 9, 3196-3207.
- YAMACI, R. F., FRASER, S. P., BATTALOGLU, E., KAYA, H., ERGULER, K., FOSTER, C. S. & DJAMGOZ, M. B. A. 2017. Neonatal Nav1.5 protein expression in normal adult human tissues and breast cancer. *Pathol Res Pract*, 213, 900-907.

- YAMAMURA, H., UGAWA, S., UEDA, T. & SHIMADA, S. 2008. Expression analysis of the epithelial Na⁺ channel delta subunit in human melanoma G-361 cells. *Biochem Biophys Res Commun*, 366, 489-92.
- YANG, D. K. & KIM, S. J. 2017. Desipramine induces apoptosis in hepatocellular carcinoma cells. *Oncol Rep*, 38, 1029-1034.
- YANG, J. L. & FRIEDLANDER, M. L. 2001. Effect of nifedipine in metastatic colon cancer with DNA mismatch repair gene defect. *Lancet*. England.
- YANG, M. & BRACKENBURY, W. J. 2013. Membrane potential and cancer progression. *Front Physiol*, 4, 185.
- YANG, M., JAMES, A. D., SUMAN, R., KASPROWICZ, R., NELSON, M., O'TOOLE, P. J. & BRACKENBURY, W. J. 2020. Voltage-dependent activation of Rac1 by Nav 1.5 channels promotes cell migration. *J Cell Physiol*, 235, 3950-3972.
- YANG, M., KOZMINSKI, D. J., WOLD, L. A., MODAK, R., CALHOUN, J. D., ISOM, L. L. & BRACKENBURY, W. J. 2012. Therapeutic potential for phenytoin: targeting Na(v)1.5 sodium channels to reduce migration and invasion in metastatic breast cancer. *Breast Cancer Res Treat*, 134, 603-15.
- YANG, S., ZHANG, J. J. & HUANG, X. Y. 2009. Orai1 and STIM1 are critical for breast tumor cell migration and metastasis. *Cancer Cell*, 15, 124-34.
- YILDIRIM, S., ALTUN, S., GUMUSHAN, H., PATEL, A. & DJAMGOZ, M. B. A. 2012. Voltage-gated sodium channel activity promotes prostate cancer metastasis in vivo. *Cancer Lett*, 323, 58-61.
- YIP, D., LE, M. N., CHAN, J. L., LEE, J. H., MEHNERT, J. A., YUDD, A., KEMPF, J., SHIH, W. J., CHEN, S. & GOYDOS, J. S. 2009. A phase 0 trial of riluzole in patients with resectable stage III and IV melanoma. *Clin Cancer Res*, 15, 3896-902.
- YOON, J. R., WHIPPLE, R. A., BALZER, E. M., CHO, E. H., MATRONE, M. A., PECKHAM, M. & MARTIN, S. S. 2011. Local anesthetics inhibit kinesin motility and microtentacle protrusions in human epithelial and breast tumor cells. *Breast Cancer Res Treat*, 129, 691-701.
- YUAN, S. Y., CHENG, C. L., HO, H. C., WANG, S. S., CHIU, K. Y., SU, C. K., OU, Y. C. & LIN, C. C. 2015. Nortriptyline induces mitochondria and death receptor-mediated apoptosis in bladder cancer cells and inhibits bladder tumor growth in vivo. *Eur J Pharmacol*, 761, 309-20.
- ZHANG, C., YUAN, X. R., LI, H. Y., ZHAO, Z. J., LIAO, Y. W., WANG, X. Y., SU, J., SANG, S. S. & LIU, Q. 2015. Anti-cancer effect of metabotropic glutamate receptor 1 inhibition in human glioma U87 cells: involvement of PI3K/Akt/mTOR pathway. *Cell Physiol Biochem*, 35, 419-32.
- ZHANG, H., QIAN, D. Z., TAN, Y. S., LEE, K., GAO, P., REN, Y. R., REY, S., HAMMERS, H., CHANG, D., PILI, R., DANG, C. V., LIU, J. O. & SEMENZA, G. L. 2008. Digoxin and other cardiac glycosides inhibit HIF-1 synthesis and block tumor growth. *Proceedings of the National Academy of Sciences*, 105, 19579-19586.
- ZHANG, L. & BARRITT, G. J. 2004. Evidence that TRPM8 is an androgen-dependent Ca²⁺ channel required for the survival of prostate cancer cells. *Cancer Res*, 64, 8365-73.
- ZHANG, P., LIU, X., LI, H., CHEN, Z., YAO, X., JIN, J. & MA, X. 2017a. TRPC5-induced autophagy promotes drug resistance in breast carcinoma via CaMKKbeta/AMPKalpha/mTOR pathway. *Sci Rep*, 7, 3158.
- ZHANG, P., YANG, X., YIN, Q., YI, J., SHEN, W., ZHAO, L., ZHU, Z. & LIU, J. 2016. Inhibition of SK4 Potassium Channels Suppresses Cell Proliferation, Migration and the Epithelial-Mesenchymal Transition in Triple-Negative Breast Cancer Cells. *PLoS One*, 11, e0154471.
- ZHANG, Y., CRUICKSHANKS, N., YUAN, F., WANG, B., PAHUSKI, M., WULFKUHLE, J., GALLAGHER, I., KOEPEL, A. F., HATEF, S., PAPANICOLAS, C., LEE, J., BAR, E. E., SCHIFF, D., TURNER, S. D., PETRICIOIN, E. F., GRAY, L. S. & ABOUNADER, R. 2017b. Targetable T-type Calcium Channels Drive Glioblastoma. *Cancer Res*, 77, 3479-3490.

- ZHAO, L., ZHAO, Y., SCHWARZ, B., MYSLIWETZ, J., HARTIG, R., CAMAJ, P., BAO, Q., JAUCH, K.-W., GUBA, M., ELLWART, J. W., NELSON, P. J. & BRUNS, C. J. 2016. Verapamil inhibits tumor progression of chemotherapy-resistant pancreatic cancer side population cells. *International journal of oncology*, 49, 99-110.
- ZHONG, J., KONG, X., ZHANG, H., YU, C., XU, Y., KANG, J., YU, H., YI, H., YANG, X. & SUN, L. 2012. Inhibition of CLIC4 enhances autophagy and triggers mitochondrial and ER stress-induced apoptosis in human glioma U251 cells under starvation. *PLoS One*, 7, e39378.
- ZHOU, F. M., HUANG, Y. Y., TIAN, T., LI, X. Y. & TANG, Y. B. 2018. Knockdown of Chloride Channel-3 Inhibits Breast Cancer Growth In Vitro and In Vivo. *J Breast Cancer*, 21, 103-111.
- ZHOU, Z., SONG, J., LI, W., LIU, X., CAO, L., WAN, L., TAN, Y., JI, S., LIANG, Y. & GONG, F. 2017. The acid-sensing ion channel, ASIC2, promotes invasion and metastasis of colorectal cancer under acidosis by activating the calcineurin/NFAT1 axis. *J Exp Clin Cancer Res*.
- ZHU, S., ZHOU, H. Y., DENG, S. C., DENG, S. J., HE, C., LI, X., CHEN, J. Y., JIN, Y., HU, Z. L., WANG, F., WANG, C. Y. & ZHAO, G. 2017. ASIC1 and ASIC3 contribute to acidity-induced EMT of pancreatic cancer through activating Ca(2+)/RhoA pathway. *Cell Death Dis*, 8, e2806.

Table 1. Na⁺ channel/transporter inhibitors in cancer.

Compound	Cancer target	Type of cancer
Amiloride	ENaC, NHE1	In vitro: multiple myeloma (Rojas et al., 2017), trophoblasts (Del Monaco et al., 2009). In vivo: hepatocellular carcinoma breast, gastric, colon, pancreatic (Matthews et al., 2011, Sparks et al., 1983).
Bupivacaine	VGSC, K _v 11.1	In vitro: breast (Chang et al., 2014, Li et al., 2018), colon (Li et al., 2019), ovarian, prostate (Xuan et al., 2016).
Carbamazepine	VGSC	In vitro: prostate (Abdul and Hoosein, 2001), breast (Teichmann et al., 2014, Meng et al., 2011), neuroblastoma (Lang et al., 1993).
Casein kinase 1 inhibitor IC261	VGSC	In vitro & in vivo: pancreatic cancer (Brockschmidt et al., 2008).
Desipramine	VGSC	In vitro: hepatocellular carcinoma (Yang and Kim, 2017), colon (Arimochi and Morita, 2008), multiple myeloma (Biber et al., 2018).
Diclofenac	VGSC	In vitro and in vivo: colon, ovarian, neuroblastoma fibrosarcoma (Pantziarka et al., 2016). In vivo: breast, lung, connective tissue tumours, prostate, pancreatic, (clinical trials) (Pantziarka et al., 2016).
Digitalis drugs (ouabain, digoxin, bufalin)	Na ⁺ /K ⁺ ATPase	In vitro: lung (Pongrakhananon et al., 2013, Lin et al., 2015), breast, colon, prostate, hepatocellular (Gould et al., 2018, Khajah et al., 2018, Shen et al., 2020, Zhang et al., 2008), osteosarcoma (Menger et al., 2012). In vivo: breast (Gould et al., 2018), lymphoma, leukaemia (Zhang et al., 2008, Haux et al., 2001), fibrosarcoma, colon, hepatocellular, head and neck (Menger et al., 2012).
Disopyramide	VGSC	In vitro: breast (Fraser et al., 2005)
Dronedarone	VGSC	In vitro: ovarian (Meléndez et al., 2020). In vitro & in vivo: breast (Elliott et al., 2018).
Imipramine/ chlomipramine/ derivatives	VGSC, K _v 10.1, K _v 11.1	In vitro: acute myeloid leukaemia (Xia et al., 1999, Metts et al., 2017), colon (Arimochi and Morita, 2006), melanoma (Gavrilova-Ruch et al., 2002, Parker et al., 2012), multiple myeloma (Biber et al., 2018). In vivo: breast (Rajamanickam et al., 2016).
Lamotrigine	VGSC	In vitro: neuroblastoma (Lang et al., 1993). In vivo: prostate (Stettner et al., 2012), breast (Pellegrino et al., 2018).
Levobupivacaine	VGSC, K _v 11.1	In vitro: colon (Li et al., 2019), breast (Li et al., 2018), prostate (Jose et al., 2018).
Lidocaine	VGSC	In vitro: breast (Yoon et al., 2011, Chang et al., 2014), colon (Siekmann et al., 2019), lung (Onganer and Djamgoz, 2005). In vivo: breast (Chang et al., 2014).
Mexiletine/ RS100642	VGSC, K _v 11.1	In vitro: breast (Fraser et al., 2005).
Nortriptyline	VGSC, K _v 11.1	In vitro: melanoma (Parker et al., 2012), multiple myeloma (Biber et al., 2018). In vivo: bladder (Yuan et al., 2015).
Phenytoin + analogues	VGSC	In vitro: breast (Yang et al., 2012), prostate (Abdul and Hoosein, 2001, Anderson et al., 2003, Fraser

		et al., 2003b), lung (Onganer and Djamgoz, 2005), neuroblastoma (Lang et al., 1993). In vivo: breast (Nelson et al., 2015).
NESOpAb	Neonatal Na _v 1.5	In vitro: breast (Brackenbury et al., 2007, Chioni et al., 2005).
Propranolol	VGSC	In vitro: breast (Lee et al., 2019a).
Protriptyline	VGSC	In vitro: osteosarcoma (Su et al., 2016), prostate (Chang et al., 2015).
Quinidine	VGSC, VGKC, K _{ATP}	In vitro: glioma (Ru et al., 2015), breast (Wonderlin et al., 1995). In vivo: breast (Raderer et al., 1993).
Ranolazine	VGSC	In vitro: breast (Driffort et al., 2014, Lee et al., 2019a), colon (Guzel et al., 2019). In vivo: prostate (Bugar et al., 2019), breast (Driffort et al., 2014).
Riluzole	VGSC, metabotropic glutamate receptor 1, K _v 11.1, K _{2P}	In vitro: prostate (Abdul and Hoosein, 2002b, Akamatsu et al., 2009, Uzun et al., 2017), pancreatic (Sun et al., 2019), neuroblastoma, glioma, lung, colon, leukaemia, myeloma (Lemieszek et al., 2018, Benavides-Serrato et al., 2020, Pillozzi et al., 2018, Poupon et al., 2018). In vivo: breast (Speyer et al., 2012), melanoma (Yip et al., 2009), glioma (Zhang et al., 2015), glioblastoma (Benavides-Serrato et al., 2020) hepatocellular carcinoma (Seol et al., 2016).
Ropivacaine	VGSC, K _v 11.1	In vitro: colon (Baptista-Hon et al., 2014), breast (Li et al., 2018)
Tarantula peptide toxin HNTX-III	VGSC	In vitro: prostate (Chen et al., 2019).
Tetracaine	VGSC	In vitro: breast (Yoon et al., 2011).
Tetrodotoxin	VGSC	In vitro: prostate (Grimes et al., 1995, Grimes and Djamgoz, 1998). In vivo: prostate (Yildirim et al., 2012).
Topiramate	VGSC	In vitro: ovarian (Xu et al., 2018). In vivo: lung (Ma et al., 2011).
Valproic acid	VGSC	In vitro: prostate (Abdul and Hoosein, 2001, Angelucci et al., 2006) breast (Olsen et al., 2004). In vivo: colon, prostate, gastro-oesophageal (Wheler et al., 2014).
ω-3 polyunsaturated docosahexaenoic acid	VGSC, NHE1	In vitro: breast (Isbilen et al., 2006, Gillet et al., 2011, Wannous et al., 2015).

Abbreviations: ENaC, epithelial Na⁺ channel; NHE1, Na⁺/H⁺ exchanger-1; VGKC, voltage-gated K⁺ channel; VGSC, voltage-gated Na⁺ channel.

Table 2. K⁺ channel inhibitors in cancer.

Compound	Cancer target	Type of cancer
4-aminopyrimidine	VGKC, K _{Ca} 2.3	In vitro: breast (Potier et al., 2006), prostate (Fraser et al., 2003a), melanoma (Artym and Petty, 2002), cervical, ovarian (Han et al., 2007).
Amiodarone	K _v 1.3, K _v 10.1, VGSCs	In vitro: prostate (Abdul and Hoosein, 2002a), breast (Abdul et al., 2003), glioma (Kim et al., 2011, Chang et al., 2018). In vivo: breast (Lee et al., 2015).
Anandamide	K _{2P} 3.1, K _v 1.2	In vitro: lung (Leithner et al., 2016), breast (De Petrocellis et al., 1998, Laezza et al., 2012), hepatocellular (Xie et al., 2012). In vivo: breast (Grimaldi et al., 2006).
Antibodies	K _v 10.1, K _v 11.1, K _{2P} 9.1	In vitro: ovarian, neuroblastoma (Gómez-Varela et al., 2007), prostate (Hartung et al., 2011), pancreatic (Sette et al., 2013, Duranti et al., 2018), breast, colon (Duranti et al., 2018), B cell lymphoma (Wang et al., 2007), lung (Sun et al., 2016). In vivo: breast and pancreatic (Gómez-Varela et al., 2007), pancreatic (Duranti et al., 2018), lung (Sun et al., 2016).
Apamine	K _{Ca} 2.3	In vitro: breast (Potier et al., 2006).
APETx4	K _v 10.1	In vitro: neuroblastoma, melanoma, prostate (Moreels et al., 2017b).
Astemizole	K _v 10.1, K _v 11.1	In vitro: lung (Chavez-Lopez et al., 2017), prostate (Bernal-Ramos et al., 2017), breast, hepatocellular (García-Quiroz et al., 2012, de Guadalupe Chavez-Lopez et al., 2015). In vivo: breast (García-Quiroz et al., 2014), hepatocellular (de Guadalupe Chavez-Lopez et al., 2015).
Bicalutamide	K _{Ca} 1.1	In vitro: breast (Khatun et al., 2018).
Calcitriol/Calcipotriol	K _{Ca} 1.1, K _v 10.1	In vitro: breast (García-Quiroz et al., 2012, Khatun et al., 2016, Khatun et al., 2018) hepatocellular (García-Quiroz et al., 2012). In vivo: breast (García-Quiroz et al., 2014).
Charybdotoxin	K _v 1.3	In vitro: prostate (Fraser et al., 2003a).
Cisapride	K _v 11.1	In vitro: gastric (Shao et al., 2005).
Clofazimine	K _v 1.3	In vitro: melanoma, lymphocytes, (Leanza et al., 2012, Leanza et al., 2013b). In vivo: melanoma (Leanza et al., 2012).
Clotrimazole	K _{Ca} 3.1	In vitro: colon (De Marchi et al., 2009), breast (Zhang et al., 2016), pancreatic (Bonito et al., 2016).
Dequalinium	K _v 1.3	In vitro: prostate (Abdul and Hoosein, 2002a).
Ergtoxin	K _v 11.1	In vitro: ovarian (Asher et al., 2011).
E4031 and Way123,398	K _v 11.1	In vitro: breast (Lansu and Gentile, 2013), ovarian (Asher et al., 2011), acute lymphoblastic leukaemia (Pillozzi et al., 2011), gastric (Crociani et al., 2014), colon (Crociani et al., 2013). In vivo: acute lymphoblastic leukaemia (Pillozzi et al., 2011) gastric (Crociani et al., 2014), colon (Crociani et al., 2013).
Enzalutamide	K _{Ca} 1.1	In vitro: breast (Khatun et al., 2018)
Glyburide	K _{ATP} , K _v 1.3	In vitro: prostate (Abdul and Hoosein, 2002a).
Iberiotoxin	K _{Ca} 1.1	In vitro: cervical, ovarian (Han et al., 2007), glioma (Weaver et al., 2004).

Imipramine	K _v 10.1	In vitro: ovarian (Asher et al., 2011).
Macrolide antibiotics	K _v 11.1	In vitro and in vivo: leukaemia (Pillozzi et al., 2016).
Margatoxin	K _v 1.3	In vitro: prostate (Fraser et al., 2003a).
Methanandamide	K _{2P} 9.1	In vitro: ovarian (Innamaa et al., 2013).
Psora-4	K _v 1.3	In vitro: melanoma, lymphocytes (Leanza et al., 2012, Leanza et al., 2013b).
5-(4-phenoxybutoxy) psoralen	K _v 1.3	In vitro: melanoma, lymphocytes (Leanza et al., 2012, Leanza et al., 2013b).
Purpurealidin analogues	K _v 10.1	In vitro: neuroblastoma, prostate, melanoma (Moreels et al., 2017a).
Ruthenium red	K _{2P} 9.1	In vitro: lung (Leithner et al., 2016).
Tamoxifen	K _v 11.1	In vitro and in vivo: breast (Luveta et al., 2020).
Tetraethylammonium	K _{Ca} 2.3, K _v 1.3	In vitro: breast (Potier et al., 2006), prostate (Fraser et al., 2003a), melanoma (Artym and Petty, 2002), cervical, ovarian (Han et al., 2007).
TRAM-34	K _{Ca} 3.1	In vitro: lymphoma (Wang et al., 2007), breast (Zhang et al., 2016), pancreatic (Zhang et al., 2016), glioma (Turner et al., 2014), colon (De Marchi et al., 2009), melanoma (Quast et al., 2012).
Verapamil	K _v 1.3	In vitro: melanoma (Artym and Petty, 2002), prostate (Fraser et al., 2003a).

Abbreviation: VGKC, voltage-gated K⁺ channel.

Table 3. Ca²⁺ channel inhibitors in cancer.

Compound	Cancer target	Type of cancer
2-Aminoethoxydiphenyl Borate (2-APB)	TRP	In vitro: breast (Hopkins et al., 2015), glioma (Bomben and Sontheimer, 2008, Bomben and Sontheimer, 2010).
Bepridil	VGCC	In vitro: breast (Park et al., 2016, Nguyen et al., 2017) glioma (Kim et al., 2011). In vivo: breast (Park et al., 2016)
Cannabinoids	TRPM8 (inhibited), TRPV1 (activated)	In vitro: colon (Borrelli et al., 2014), cervical, glioma (Contassot et al., 2004a, Contassot et al., 2004b), breast (Ligresti et al., 2006), neuroblastoma (Hamtiaux et al., 2011). In vivo: colon (Borrelli et al., 2014)
Capsazepine	TRPM8	In vitro: prostate (Zhang and Barritt, 2004)
Diltiazem	VGCC	In vitro: prostate (Kaddour-Djebbar et al., 2012), breast (Timar et al., 1992, Roger et al., 2004), pancreatic (Woods et al., 2015)
Felodipine	VGCC	In vitro: melanoma, breast (Honn et al., 1985) In vivo: melanoma (Honn et al., 1985)
Fendiline	VGCC	In vitro: pancreatic (Woods et al., 2015, Alhothali et al., 2019), lung, endometrial, colon (van der Hoeven et al., 2013).
Flunarizine	VGCC	In vitro: melanoma (Sezzi et al., 1985), multiple myeloma, lymphoma (Conrad et al., 2010, Schmeel et al., 2015)
Fluspirilene	VGCC	In vitro & in vivo: glioblastoma (Dong et al., 2017), hepatocellular (Shi et al., 2015).
KYS05090	VGCC	In vitro: ovarian (Jang et al., 2013). In vitro and in vivo: lung (Kang et al., 2012, Rim et al., 2014).
Mibefradil	VGCC	In vitro: leukaemia (Huang et al., 2015), breast, retinoblastoma (Bertolesi et al., 2002), colon (Dziegielewska et al., 2014), glioblastoma (Valerie et al., 2013, Zhang et al., 2017b) In vivo: glioma and glioblastoma (Holdhoff et al., 2017, Zhang et al., 2017b)
Monoclonal antibody	nfP2X7	In vivo: basal cell carcinoma (clinical trials) (Gilbert et al., 2017, Gilbert et al., 2019).
Nifedipine	VGCC	In vitro: breast (Timar et al., 1992, Roger et al., 2004, Squecco et al., 2015), melanoma (Honn et al., 1985), pancreatic (Woods et al., 2015) endometrial (Bao et al., 2012). In vivo: melanoma (Honn et al., 1985), colon (Yang and Friedlander, 2001).
Nimodipine	VGCC	In vitro: melanoma, breast (Honn et al., 1984, Honn et al., 1985). In vivo: melanoma (Honn et al., 1984, Honn et al., 1985).
NNC-55-0396	VGCC	In vitro: leukaemia (Huang et al., 2015)
20-O-β-D-glucopyranosyl-20(S)-protopanaxadiol, 4-chloro-m-cresol	Ryanodine receptor	In vitro: lung (Shin et al., 2018). In vivo: breast (Abdul et al., 2008).
Pimozide	VGCC	In vitro: breast, retinoblastoma (Bertolesi et al., 2002).
SKF96365 and MRS-1845	ORAI, TRPC1	In vitro: glioma (Bomben and Sontheimer, 2008, Bomben and Sontheimer, 2010). In vivo: breast (Yang et al., 2009).

SOR-C13, SOR-C27	TRPV6	In vivo: solid tumours of epithelial origin (Phase I Clinical Trial) (Fu et al., 2017), ovarian (Xue et al., 2018), prostate (Bowen et al., 2013).
Verapamil	VGCC	In vitro: pancreatic (Sato et al., 1994, Zhao et al., 2016), breast (Timar et al., 1992, Roger et al., 2004, Berzingi et al., 2016). In vivo: pancreatic (Sato et al., 1994, Zhao et al., 2016).
Waixenicin A	TRPM7	In vitro and in vivo: colon (Huang et al., 2017).

Abbreviations: TRP, transient receptor potential, VGCC, voltage-gated Ca^{2+} channel.

Table 4. Cl⁻ channel inhibitors in cancer.

Compound	Cancer target	Type of cancer
Ani9 and derivatives	ANO1	In vitro: prostate (Song et al., 2018), pancreatic, breast (Seo et al., 2018).
Bumetanide	NKCC1	In vitro & in vivo: glioma (Haas and Sontheimer, 2010), colon (Malamas et al., 2015).
CaCCinh-A01	ANO1	In vitro: prostate (Song et al., 2018), colon, lung (Guan et al., 2016), breast (Britschgi et al., 2013), oesophageal and pharyngeal squamous carcinoma (Bill et al., 2014), pancreatic (Sauter et al., 2015).
Chlorotoxin	CLC-3	In vitro and in vivo (clinical trials): glioma (Deshane et al., 2003, Mamelak et al., 2006)
DIDS	Acid-induced Cl ⁻ channels	Nasopharyngeal (Wang et al., 2012)
Digallic Acid and Tannic Acid	ANO1	In vitro: lymphoblastoma (Bhouri et al., 2012), oesophageal and pharyngeal squamous carcinoma (Bill et al., 2014), gingival (Darvin et al., 2015), breast (Nie et al., 2016), prostate (Karakurt and Adali, 2016)
Idebenone	ANO1	In vitro: pancreatic, prostate (Seo et al., 2015)
Luteolin	ANO1	prostate (Seo et al., 2017)
NPPBs	Acid-induced Cl ⁻ channels	In vitro: cervical (Shen et al., 2000), nasopharyngeal (Wang et al., 2012)
Tamoxifen	Acid-induced Cl ⁻ channels (CLC-3)	In vitro: hepatocellular (Mao et al., 2013), cervical (Shen et al., 2000), nasopharyngeal (Wang et al., 2012). In vivo: breast (Luveta et al., 2020)
T16Ainh-A01	ANO1	In vitro: pancreatic (Mazzone et al., 2012), prostate (Song et al., 2018), colon, lung (Guan et al., 2016), oesophageal and pharyngeal squamous (Bill et al., 2014), pancreatic (Sauter et al., 2015).

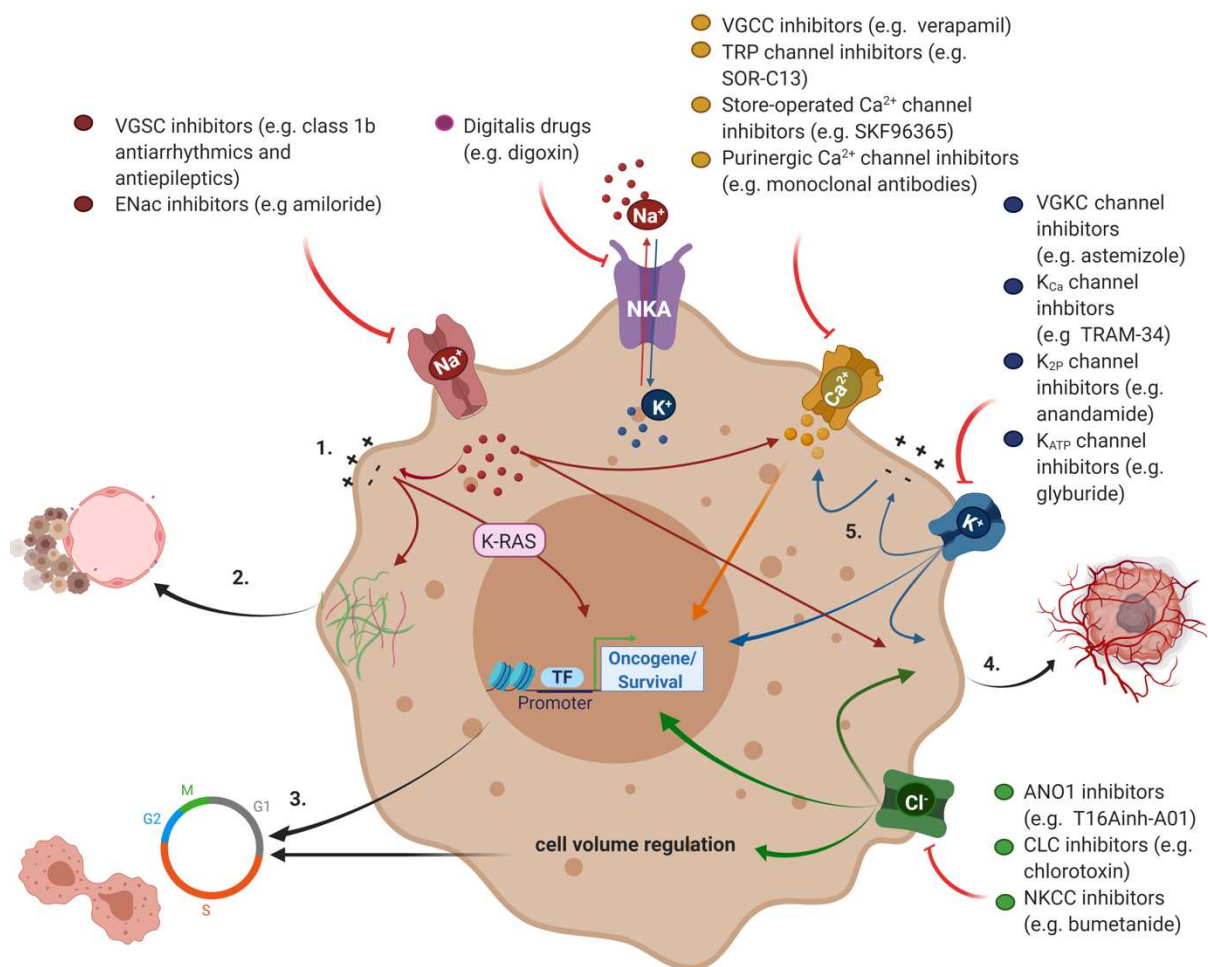


Figure 1. Potential anticancer utility of Na⁺, K⁺, Ca²⁺ and Cl⁻ channel blockers. Principal consequences of ion channel function in cancer cells: (1) Membrane potential depolarisation (Yang and Brackenbury, 2013); (2) invasion and metastasis (Besson et al., 2015); (3) cell cycle progression and proliferation (Becchetti, 2011); (4) angiogenesis (Fiorio Pla et al., 2012); (5) Ca²⁺ signalling in response to altered K⁺ channel activity (Illek et al., 1992). Na⁺, Ca²⁺, K⁺ and Cl⁻ channels are represented on the plasma membrane for clarity, but some functions are performed by intracellularly located channels (details in main text). Key inhibitor classes and examples of widely studied compounds are included (see Tables for a complete list). Abbreviations: ENaC – epithelial Na⁺ channel, K_{Ca} – Ca²⁺ dependent K⁺ channels, K-

RAS - Kirsten rat sarcoma, NKA - Na^+/K^+ ATPase, NKCC – $\text{Na}^+/\text{K}^+/\text{Cl}^-$ co-transporter, TF – transcription factors, VGCC – voltage-gated Ca^{2+} channel, VGKC – voltage-gated K^+ channel, VGSC – voltage gated Na^+ channel.